THE MEDICAL JOURNAL OF AUSTRALIA

VOL. I.—40TH YEAR SYDNEY, SATURDAY, MAY 9, 1953 No. 19

Table of Contents.

ORIGINAL ARTICLES— Page.

The Jackson Lecture—Genes and Mermaids, Changing Theories of the Causation of Congenital Abnormalities, by M. F. Hickey 649

REPORTS OF CASES—

Coarctation of Aorta with Multiple Congenital Abnormalities, by Harry M. Windsor 668

Advanced Chronic Endocarditis with Mitral Stenosis and Aortic Stenosis in a Child of Three Years, by Bryan Sharkey and Vincent J. McGovern 668

A Traumatic Gap in the Urethra, by V. H. Wallace 669

REVIEWS—

The Emergency Medical Services 670
Dermatology 671
Diseases of the Ear, Nose and Throat 671
Laboratory Manual of Physiological Chemistry .. 671
Principles and Practice of Obstetrics 671
The 1952 Year Book of Drug Therapy 671
The 1952 Year Book of Pediatrics 672
Advances in Internal Medicine 672

NOTES ON BOOKS, CURRENT JOURNALS AND NEW APPLIANCES—

Family Doctor 672

BOOKS RECEIVED 672

LEADING ARTICLES—

American Light on Voluntary Health Insurance .. 673

CURRENT COMMENT—

The Control of Bowel Emptying 674
The Ballistocardiogram 675

ABSTRACTS FROM MEDICAL LITERATURE— Page.

Ophthalmology 676
Oto-Rhino-Laryngology 677

SPECIAL ARTICLES FOR THE CLINICIAN—

LXII. Piles or Hæmorrhoids 678

MEDICAL SOCIETIES—

The Medical Defence Society of Queensland 682

OUT OF THE PAST 683

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA 683

POST-GRADUATE WORK—

The Post-Graduate Committee in Medicine in the University of Sydney 683

UNIVERSITY INTELLIGENCE—

University of Melbourne 684

CORRIGENDUM 684

DEATHS 684

ROYAL AUSTRALASIAN COLLEGE OF SURGEONS—

Open Meeting 684

MEDICAL APPOINTMENTS 684

NOMINATIONS AND ELECTIONS 684

DIARY FOR THE MONTH 684

MEDICAL APPOINTMENTS: IMPORTANT NOTICE .. 684

EDITORIAL NOTICES 684

The Jackson Lecture.[1]

GENES AND MERMAIDS: CHANGING THEORIES OF THE CAUSATION OF CONGENITAL ABNORMALITIES.[1]

By M. F. HICKEY,

Department of Anatomy, University of Queensland.

Under the circumstances, progress towards a real understanding of these problems will best be furthered by keeping our minds open to all the possibilities and alert for further trustworthy evidence (Bradley M. Patten).

INTRODUCTION.

IT is just twenty years since the first Jackson Lecture was delivered, in September, 1931, by Dr. Sandford Jackson himself. Consequently, it seems fitting that now, after two decades, we should recall for a moment the genesis of this annual lecture in medical history which was established by the Council of the Queensland Branch of the British Medical Association in order to put on permanent record its appreciation of the distinguished services to the Branch of Dr. Ernest Sandford Jackson over a very extended period of time, and which it is my privilege to give this evening.

The high regard in which Dr. Jackson was held by his colleagues is indicated firstly by the fact that the annual lecture in his honour was instituted during his lifetime (he died at Brisbane on June 29, 1938); and further, Dr. Jackson was himself invited to give the first Jackson Lecture, which he did, taking as his subject "Some Voyages Connected with the Discovery of Australia: Their Medical History". Since then, a distinguished series of lecturers, both from Queensland and from the southern States, have dealt with many aspects of medical history—from prehistory and classical antiquity down to modern hospitals and preventive medicine: the contemplation of this distinguished company and the study of their addresses make me conscious of my own shortcomings and diffident about appearing before you as a Jackson Lecturer.

The Genesis of this Lecture.

First let me give a brief explanation of the title of my address. Some years ago, through the good offices of Dr. J. F. Dunkley, of Brisbane, and Dr. Wilfred Simmonds, now of the Kanematsu Institute, Sydney, there came into my hands for dissection an abnormal fœtus of nearly full-term, of the very rare variety known as *sympus dipus* (with fused legs, showing elements of two fused feet); also called *symmelus*, or *sirenomelus*, and more usually a "mermaid" (Figure I).

My search for the possible ætiology of the condition has led me into many fields of study, from the folk-lore of antiquity down to modern investigations of morphogenesis, as I sought some reasonable explanation for the occurrence of gross abnormalities in general and of this one in particular. And as my address will show, this search has so far led me to consider for the "mermaid" (really a "merman") the implications of the modern theory of the gene and its mutations as a possible basis of explanation: hence the title "Genes and Mermaids".

[1] Delivered at a meeting of the Queensland Branch of the British Medical Association on September 7, 1951. It is regretted that the publication of this address has been unavoidably delayed.

To give a starting point to my discussion, I should like first to outline and illustrate for you the principal features of this abnormal form, the Brisbane specimen of *sympus dipus*. As you see from my drawings of this specimen (Figure I), sympodia is a condition characterized by a more or less complete union of the lower limbs; the patellæ either laterally or posteriorly situated, the heel and sole of the fused feet (if present) facing anteriorly, the whole inferior extremity being flexed on the lower part of the trunk.

Another diagram (Figure II) shows the radiological findings. In the inferior extremity the two femora are fused in their whole length, the main evidence of their separate identities being seen in the two distal epiphyses of the femora. You will observe that the tibiæ are laterally disposed and the fibulæ are represented by one bone, placed between the tibiæ but on a posterior plane. The tarsus shows evidence of fusion and suppression of elements; there are seven metatarsals, five right and two left.

The vertebral column, apart from 13 thoracic vertebræ and associated ribs, shows considerable disorganization, with fusions and suppressions, in the lumbar, sacral and coccygeal regions. The pelvis, owing to the "lateral rotation" of the hip bones, is virtually non-existent as a cavity; and the acetabular sockets are fused behind, allowing the single femoral head to articulate posteriorly.

However, although the leg malformation is the striking feature, there are other skeletal and, what is more important, marked visceral malformations. A glance at my sketch of the lower abdominal viscera (Figure III) shows the dilated blindly ending colon. (Incidentally there is no anus, as the perineum would inevitably be suppressed.) There is no differentiated bladder; all we see is what I have called the "cloacal mass", into which empty the single right ureter and the two *vasa deferentia*, and to which the colon is attached by a fibrous cord. No kidneys were visible macroscopically; but the upper end of the right ureter was lost in the connective tissue of the posterior abdominal wall, in which scattered renal elements were found on histological examination. In the vascular system, no large renal arteries were present, the pelvic and leg arteries were abnormal and there was a very large single umbilical artery—normally there are two.

I may add here that the external genitalia were absent, and the left hand lacked a thumb (Figure IA).

You will agree that this is a remarkable assemblage of abnormalities—although in general careful dissection of all grossly abnormal fœtuses will reveal multiple anomalies. Since examining this specimen originally, I have had the opportunity of examining all, and dissecting several of, the known specimens of sympodia in Sydney and Melbourne (a total of ten in all). As far as my work has gone, they all show this characteristic of multiple abnormalities; that is the presence, in addition to the diagnostic skeletal abnormality, of several other abnormalities, especially of the viscera.

From the specimens I have studied and the reports I have read, the inferior extremity deformities can be arranged in a fairly regular series from the condition in which the separate bones can all be discerned, through instances of increasing fusion and suppression, to the extreme deformity in which the lower half of the body is but a cone-shaped process, the bones of the pelvis are a coalesced mass, and those of the inferior extremity are represented merely by a single short irregular shaft or stump. And in most specimens at all fully described there are several other major anomalies, especially visceral.

May I then emphasize these two features characteristic of the many cases—(*a*) the multiple abnormalities in several systems, and (*b*) the fairly continuous gradation of abnormality of the lower extremities; I shall have occasion to refer to these features later.

Definitions.

First, as to the scope of the expression "congenital abnormality": congenital means existing at birth; and abnormality implies a situation deviating from the type, contrary to rule or system. Abnormality could be replaced by anomaly, meaning deviation from the common or natural order, but neither of these terms is limited to structure. The term malformation (or deformity) means any gross anatomic deviation from the normal; but although it is often used interchangeably with anomaly and abnormality, this is not sound practice, for a congenital abnormality will embrace not only malformations externally obvious and also the concealed abnormalities of the body organs, but, indeed, it should also include those inborn errors of function (for example, alkaptonuria) and hereditary tendencies to disease (for example, Huntington's chorea) which are objects of study of medical genetics. Obviously the word "monster" (nowhere well defined) will denote a grosser form of malformation but only a minor case of all congenital abnormalities.

The Historical Scheme.

I have attempted to arrange my account of the theories of teratogenesis in some sort of chronological order by considering them under three principal periods: antiquity; the seventeenth to nineteenth centuries; and the twentieth century; but I should point out that this arrangement is to some extent a matter of convenience in treatment, and it will be seen that I do not at all rigidly adhere to the division, especially where it would cause the account to become too disjointed.

I. Theories of Antiquity.

Supernatural Causes.

In the literature and legends of the past and in the customs and beliefs of present-day savage peoples there is abundant evidence that, in the primitive stages of man's existence, it is customary to attribute all unusual phenomena, such as earthquakes, comets, eclipses and so on, to supernatural causes—gods, evil spirits, and the like. And we shall not be surprised to find in the earliest records of teratology indications that bodily abnormalities were regarded as due to supernatural agencies, including the moon and the stars.

I cannot here omit to mention the elder Pliny (A.D. 23-79), whose vast work, the "Natural History", of encyclopædic scope far beyond what we would call "natural history", with its strange mixture of fact and fancy, influenced students for fifteen hundred years; for Pliny epitomizes these supernaturalist theories in his naïve animistic conception of the causation of monstrosities: "*Ludibria sibi, miracula nobis ingeniosa facit natura*—Ingenious nature creates monsters for the purpose of astonishing us and amusing herself". And it is with the credulous and voluble Pliny that we appear to find the first mention of the sympodial or sireniform abnormality from which this story of mine has its origin; for in Book 7, Chapter II, he repeats the sailor's yarn that there existed somewhere near the country of the Troglodytes, a race of men called Monocoli, who, although possessed of only one median limb, were able to walk and jump about with great agility. These beings, says our author, were accustomed to recline on their backs during the heat of the sun, and to protect themselves from its rays by their over-spreading feet!

But to return to the question of supernatural causes: putting aside for the moment the theories of lunar and stellar influences, it is interesting and chastening to observe how many men famous in the history of anatomy, surgery and the like even down into the nineteenth century regarded divine intervention as a possible cause of monstrosity—Ambroise Paré in the sixteenth century, Régis in the seventeenth, Winslow in the eighteenth, and, strangely enough in the early twentieth century, Étienne G. Saint-Hilaire, the founder of modern classificatory teratology.

Forbidden Times.

The fantastic belief that intercourse during the menstrual period could be a cause of monster-formation is found among the ancient Hebrews and Romans. And the belief persisted amongst learned men till towards the close of the seventeenth century, when from the investigations of Harvey and de Graaf, and from the light which they threw upon the true nature of the female factor in reproduction,

the menstrual theory of teratogenesis received its death-blow.

Natural Causes.

However, I should be giving a very false view of the history of embryology if I left you with the idea that the only teratogenic theories of the ancient world were those which recognized supernatural agencies. The fact is that the early Greek philosophers looked for purely physical causes of monstrosities, and they found these in the disturbances of the natural phenomena of reproduction. But their theories were founded on erroneous interpretations of fact and on mistaken observations, and their ideas of abnormal development would be erroneous, as were many of their theories of development.

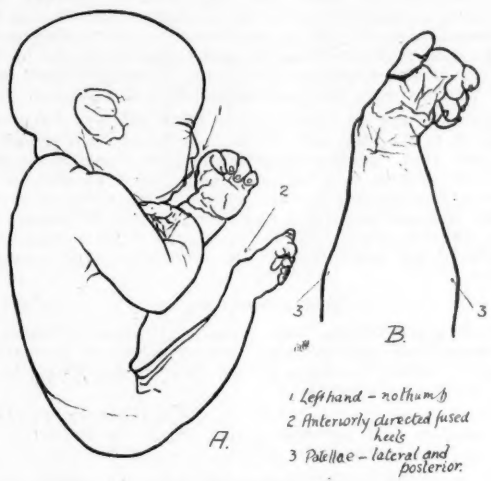

FIGURE I.

Sympus dipus (Brisbane specimen). A. Lateral view of whole fœtus showing marked flexion of fused inferior extremities on trunk. B. Anterior view of fused inferior extremities.

With the invention of the microscope 2000 years in the future, nothing was known of human ova and spermatozoa. To the Greek, the evident facts of the generative process were the seminal discharge of the male and the menses of the female. The importance ascribed to either or both of these elements varied and so also varied the teratogenic theories. But it was soon recognized that both parents might supply abnormal factors, and this was the view of Aristotle.

I must resist the temptation to speak at any length of the many-sided genius and the prodigious works of this remarkable man of the fourth century B.C. With him general or comparative biology came into its own. His enormous contributions to embryology and their profound influence down to modern times have been well described by Needham in "A History of Embryology" (1934): "Embryology from the third century B.C. to the seventeenth century A.D. is meaningless unless it is studied in the light of Aristotle."

As to teratology, Aristotle was the founder of both human and comparative teratology, for he made the earliest systematic attempt to explain the origin of human and other monstrosities in his work "On the Generation of Animals". His definition of monstrosities reveals an extraordinary degree of critical insight:

> The monstrosity is contrary to nature, not contrary to nature taken absolutely, but contrary to the most usual course of nature. Nothing, in fact, can be produced contrary to that nature which is both eternal and essential.

Aristotle discussed in a truly scientific manner the theories of teratogenesis current in his time; he found the origin of monstrosities in the conjoint action of perverted states of both male and female elements in generation. This theory may rightly be called the Aristotelian theory. In his work and in the Hippocratic writings are found the roots, so to speak, of the belief in the teratogenic power of traumatism and pressure acting upon the embryonic organism, and, in Aristotle's view, pressure acting at a very early stage in germinal or embryonic life; but more than two thousand years were to pass before the tree blossomed out into the full growth of the nineteenth century theory of the production of malformations by mechanical influences. Aristotle's writings indicated the high-water mark of teratological knowledge, both human and comparative, for more than two thousand years; and it is only in the last century or so, with all the modern

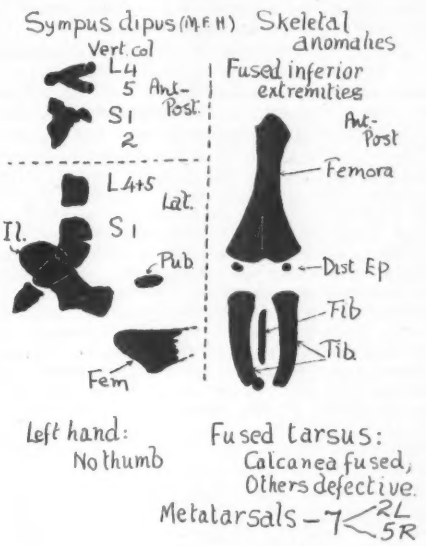

FIGURE II.

Sympus dipus (Brisbane specimen): skeletal anomalies as determined radiologically.

methods of research at our command, that we have advanced the subject far beyond the point at which Aristotle left it. Such mistakes as Aristotle made, and naturally he made many, were not so important as the solid ground gained by his correct answers, for they were always open to experimental test, even though the authority of his name virtually precluded this until the Renaissance.

He died in 322 B.C.; from that year until 1534, the date of the birth of Volcher Coiter, first in time of the Renaissance embryologists, embryology has very little history and scientific teratology even less.

II. Theories of the Seventeenth to Nineteenth Centuries.

Maternal Impressions.

Any survey of the history of teratological theory would be incomplete, in regard to both historical perspective and bulk of the discussion, which omitted any consideration of the theory of maternal impressions. Only four years ago Bradley Patten in his "Human Embryology" (1947) wrote:

> It is astonishing how many people believe that a fright or an unpleasant sight during pregnancy will cause a child to be marked in a manner suggesting the incident.

Indeed, the whole history of these theories illustrates the truth of Osler's dictum: "In all things relating to disease, credulity remains a permanent fact, uninfluenced by civilisation or education."

The crude maternal impression theory claims that there is a marked (even absolute) similarity between the thing producing the impression and the defect or anomaly result-

ing therefrom. The notion is of great antiquity, it was of practically worldwide distribution, and the authority of the supporters of the belief was great indeed. It is not for me, to this audience, to set about the task of pointing out the erroneous nature of the beliefs.

A survey of the origin and growth of this ancient and well-nigh universal doctrine (Ballantyne, 1902-1904) shows us that in its earliest beginnings it was not specially a teratogenic theory, but rather one used to explain how the young of men and of animals came to be of special colours or hairiness, and particularly of a tint or degree differing from that of their parents; then it was accepted as the solution of the origin of mothers' marks or nævi; then as a possible explanation of the birth of infants with hypertrichosis; and, finally, it came to be applied, and in most ingenious ways, to account for almost every kind of anomaly, malformation and monstrosity.

The idea of the influence of maternal impressions is as old as the Old Testament, for in Genesis xxx, 35-42, we learn of Jacob's artifice by means of which he acquired a large number of speckled cattle of a vigorous breed.

It would delay us too long to trace the history of this theory through classical antiquity, the Middle Ages and the Renaissance, down to the dawn of modern science. The number and variety of the claims made by the sixteenth century writers, including such men as Martin Luther and Ambroise Paré, bear testimony to the fecund imagination and credulity of man. The most fanciful applications of the theory were extended to all forms of monstrosity as well as to minor manifestations of malformation. And in the succeeding century (the seventeenth) the maternal impression theory reigned supreme amongst scientists such as Bartholin, Swammerdam and even Boyle, whose mind conceived the law of the relation between pressure and volume of a gas. Of course, it could only be with the gradual dispersal of the relative ignorance of the gross physiology of generation and of intrauterine life in the seventeenth and eighteenth centuries that we would expect a change in the beliefs of medical men.

However, there were signs of the beginnings of a rational criticism even as early as the first part of the seventeenth century, although towards the close of that century the examples of credulity multiplied greatly. The first sign of the new attitude was that men of science began to attempt to give a physiological explanation of the *modus operandi* of maternal impressions. We should remember that it was only in 1651, just three hundred years ago, that William Harvey's great work *"Exercitationes de Generatione Animalium"* appeared in Latin; a work, which, embodying Harvey's careful experimental observations on the deer, his clinical observations and his acute reasoning, by itself would have made him famous. In this work he denied any anastomotic connexion between the maternal and fœtal circulations.[1]

In the eighteenth century a sceptical criticism of the old beliefs developed amongst scientists or, at least, some of them, for the discoveries of the close of the seventeenth century had done much to clear up many of the vexed questions of reproduction and antenatal physiology. A most vigorous blow against the impression doctrine was struck by the English physician, Blondel, in 1727, when he showed that the "imaginatist" theory was unsupported by experience, by reason and by anatomy; and the arguments against imaginationism were established on more scientific grounds by Albrecht Haller in 1766, as, for example, that there was no demonstrable nervous connexion between mother and fœtus.

[1] "In the Cæsarean section, also, it is quite clear that the life of the embryo does not immediately depend upon the mother, ... Besides, in a tedious labour we learn whether the infant is alive or not by the pulsation of the umbilical arteries; and it is certain that these arteries receive their impulse from the heart of the fœtus and not of the mother, for the rhythm of the two differs: this can be easily ascertained if one hand is applied to the wrist of the mother and the other to the umbilical cord. . . . It is not, therefore, true that the 'spirits' pass from the mother to the fœtus through the arteries; nor is it more so that the umbilical or fœtal vessels anastomose with those of the uterus." Wm. Harvey, "On the Generation of Animals", in Latin (1651), trans. R. Willis (1847), The Sydenham Society, London.

But the victory was by no means complete and it may please you to hear that it was in the closing years of the eighteenth century that the money value of a maternal impression (of a patriotic kind!) was fixed at 400 francs *per annum*; for Saint-Hilaire records that in the third year of the French Republic an infant was born with a representation on the left breast of a Phrygian cap, symbol of liberty, and to the mother the government awarded the above sum, presumably for her patriotic thoughts.

The new attitude did not develop in a few years nor without great controversy; indeed in 1904 Ballantyne speaks of the persistence of the belief amongst medical men in Great Britain; and in 1908 we find Mall deploring the rather widespread persistence of this belief amongst American medical men. But although the belief persisted amongst medical men into the present century, the enormous advances in embryological knowledge during the nineteenth century led to the almost complete abandoning of the theory by embryologists and teratologists, for in that century Meckel placed teratology on an embryological basis and Virchow gave the histological basis to anatomy.

The only way in which the old belief has any faint echo today is in the view held by some scientists that it may be possible that "psychic trauma" in early pregnancy of a nervous woman may, through some such mechanism as uterine contraction, produce perhaps a partial detachment of the ovum or increased amniotic pressure *et cetera*. But it is difficult to see why such a chance mental impression should bring about a definite deformity (Birch-Jensen, 1949).

Mechanical Factors.

Mechanical factors will include all those theories of malformations and monstrosities being due to mechanical factors, mainly pressure, acting directly or indirectly on the developing organism.

Early evidence of a belief in the teratogenic power of traumatism and pressure acting upon the fœtus in the uterus is to be found in Hippocrates and Aristotle.

We meet the theory again in the sixteenth century in the writings of the French surgeon, Ambroise Paré, who mentions, amongst others, these three possible causes of monstrosities—(*a*) narrowness of the uterus, (*b*) faulty posture of the pregnant woman, and (*c*) external violence (such as a fall) affecting the fœtal bones or opening a vein with the result that the infant is undernourished and small or altogether monstrous.

In the following centuries many other writers expressed very much the same views, in general merely adding to the list of pressure agencies, though these theories were not uncritically accepted. In the closing years of the eighteenth century there was a distinct diminution in the popularity of the pressure theory among medical men, a change in opinion to which Morgagni greatly contributed by propounding the idea that fœtal diseases, as, for example, the accumulation of fluid in the body cavities, are the direct causes of monstrosities (see later).

Nevertheless, in the nineteenth century there was a great revival of the mechanical action theory, and although it was strongly controverted by Meckel and others, it became more and more elaborated and more widely accepted, so that by the end of the century the doctrine in its scientific form was regarded by many workers as adequate and satisfactory.

Leaving aside all extrauterine pressure theories, we may briefly note the support for the idea of intrauterine pressure in which the embryo or fœtus may be acted upon by various structures lying inside the uterus (for example, uterine polpyus, twin pregnancies with *fœtus compressus*), or be subjected to pressure by its own parts, as by a limb. It is extremely doubtful whether any of these causes could produce monstrosities, even though some case could be made out for the production of minor malformations.

Another theory which had a considerable vogue and led to much controversy during the nineteenth century (and after) is that of the teratogenic effects of pressure by the umbilical cord (funic pressure), which was supposed to

operate either by causing pressure of one part of the body on another or by encircling and constricting one of the parts of the unborn infant.

Various objections were raised to this funic theory during last century. About 1830 Montgomery suggested that spontaneous amputations and circular depressions of fœtal limbs were due to the constricting effects of fine threads of lymph, and not of the cord. One difficult question was the occasional occurrence on the ends of the stumps of these apparently spontaneously amputated limbs of little projections, at times bearing nails. Again, in 1851, Gatty reasonably pointed out that while the cord might constrict the limb it could not amputate it, because the pressure on the cord itself would be so great as to stop the circulation and so kill the fœtus.

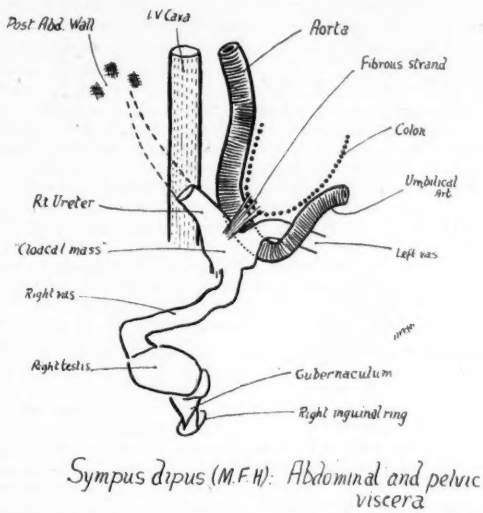

FIGURE III.

In spite of these and similar objections, the funic theory still commanded considerable support at the end of the nineteenth century.

Fœtal Disease.

The theory that diseases of the fœtus are causes of monsters was first put forward by the great Morgagni early in the eighteenth century; and later in his *"De sedibus et causis morborum"* (1761) he attempted to frame a rational and scientific explanation of the possible *modus operandi* of fœtal diseases as the causes of monsters by deficiency. Morgagni first put forward the suggestion of hydrocephalus as a cause of anencephaly, and this ingenious suggestion attracted numerous and authoritative supporters. An interesting indication of the state of physiological knowledge of the time is seen in the fact that some scientists could not understand how the fœtus could have lived *in utero* without the brain which furnished the "animal spirits".

Again, fœtal peritonitis was suggested as a cause of monstrosities, including those of arrested development; and in 1880 Guerin expounded his theory that a large number of monstrosities and malformations, including suppressions, arrests and perversions of development, were due to one great cause—an affection of the cerebro-spinal system.

It was the unjustifiable extension of this fœtal nosological theory to explain most monstrosities and malformations which suggested its defects and aroused a strong criticism throughout the nineteenth century by many workers including the Saint-Hilaires, Virchow, Dareste and others. Virchow rightly insisted that both the pressure theory as commonly held and the theory of diseases as the causes of monstrosities were founded upon erroneous conceptions of embryogenesis. Indeed it was not until well into the second half of the nineteenth century that His established the details of the early development of the embryo.

Adnexal Disorders—The Amnion.

The transition from the idea of fœtal disease to that of fœtal adnexal diseases as causes of monstrosity is an easy one. And of the adnexa, amnion and chorion, yolk sac, allantois, the only one of importance is the amnion.

The amniotic theory of teratogenesis was developed during the nineteenth century as a result of many obstetrical observations and much experimentation in the production of monsters. And, as a result, in the pathology of the embryo, by about 1900 the amnion was believed to occupy a dominant position. It was held to be, and by some is still thought to be, the chief cause, direct or indirect, of all those malformations or monstrosities characterized by defective development. (Compare Johns, 1946.)

You will all be familiar with cases or reports of cases in which amniotic adhesions and amniotic bands and the like were present. The material has generally been classified on a "geographical" basis, as, for example, adhesions of cranium or face to amnion, adhesions of anterior or lateral abdominal defect to amnion, and so on; and limb deformities and amputations were, under this theory, due to amniotic bands and filaments.

I may observe at this stage that in these abnormalities of supposed amniotic origin, there are generally, in addition to the obvious abnormality, several other malformations in other parts of the body which it would be difficult to ascribe to amniotic action.

It appears that the notion of amniotic adhesions as a reasonable and sufficient cause for all monstrosities was first expounded by the elder (E. G.) Saint-Hilaire in the 1820's. He saw in bands passing from the membrane to the fœtus the simple and satisfactory explanation of all monstrosities. This "blanket theory" met with immediate criticism. For example, Meckel, the advocate of the theory of developmental arrest, held that Saint-Hilaire's explanation could hold good only in a few cases; for in all Meckel's cases there had been no adhesions. Rudolph went further and maintained that adhesions were not the cause but the effects of the monstrosity of the fœtus (Ballantyne, 1902-1904)—a statement which would be accepted by many embryologists today.

Influenced probably by the criticisms to which his father's theory had been subjected, the younger (I. G.) Saint-Hilaire (1836) stated that he did not regard it as applicable to all monstrosities and anomalies, but only to those characterized by defect, by displacement, and by want of union of contiguous surfaces.

The idea of abnormalities of the limbs (spontaneous amputations and circular depressions) as caused by the constricting effects of fine bands of organized lymph due to the inflamed condition of the apposed surfaces of the fœtal skin and the amniotic membrane, was developed during the 1830's by Montgomery and Simpson. Their nosological theory was soon applied to the explanation of many other deformities. But in its strict sense it was subjected to much criticism. For example, scantiness of *liquor amnii* would seem to be a prerequisite for the formation of adhesions, for this would allow the amniotic membrane (or folds of it) to remain in contact with the fœtus; and these folds being with growth drawn out into bands would exert traction upon and so produce malformations of fœtal parts. Unfortunately for this theory, the frequent coexistence of hydramnios with monstrous fœtal conditions raises difficulties for which no satisfactory solution was forthcoming. However, even if disease-caused amniotic bands could be incriminated for malformations and monstrosities by defect, they could in no way explain monstrosities by excess and the double terata.

It is at this point that the interconnexion of theories is well demonstrated. About the middle of the nineteenth century the discoveries of the embryologists began to clarify the nature and mode of origin of all the fœtal membranes, including the amnion. It began to be recog-

nized that the amnion, in some of the lower animals at least, was formed by the upgrowth of folds (cephalic, caudal and lateral: see Figure IV A) of the blastodermic vesicle extending to meet all round the embryo and wall it in. "The suggestion naturally followed that any arrest in the development of these folds or any deviation from the normal mode of their upgrowth could lead to the establishment of abnormal relations between them and the embryo lying within them."

At first attempts were made to reconcile the idea of a developmental defect with the notion of an inflammatory disease of the amnion or the fœtus; but gradually, owing largely to results of the experimental production of monstrosities in the chick by Camille Dareste in the second half of the nineteenth century, the idea of fœtal or adnexal disease dropped out of the amniotic theory of teratogenesis. Dareste found that alteration of the environmental conditions during incubation led to the production of many abnormalities in the embryo chick; and he claimed that in most of these cases it was the development of the amnion that was at fault; that there was usually a defective secretion of *liquor amnii* or that the growth of the amnion was lagging, with the result that it remained in contact with the surface of the embryo and exercised pressure upon it.

Before the end of the nineteenth century amniotic pressure was established as the most popular theory of teratogenesis among teratologists, and with these workers it largely supplanted any notions of disease either of the fœtus itself or of the surrounding membranes.

Embryological Theory—to (about) 1900.

In general the embryological theory (or theories) of teratogenesis, which has a long but discontinuous history, would say that all or most congenital abnormalities are due to a fault inherent in the "germ plasm" itself, not to disease of the fœtus or adnexa, not to mechanical factors such as pressure, and not to abnormalities of amniotic development.

The full development of this theory from what was at first a speculative interpretation of facts or even a "last hope" explanation when other theories seemed to fail, to what is now one of the most important theories of teratogenesis, depended of course on the development of embryological knowledge.

Although Aristotle realized that abnormalities were due to both paternal and maternal factors, the embryological theory of teratogenesis in any true sense dates from the time of the great William Harvey, who in 1651 gave the first indications of the embryological theory of developmental arrest in a famous passage on malformations, which occurs in his description of conception in the deer, as part of his account of the appearance of the fœtal deer at about eight weeks:

> Towards the end of November, then, all the parts (of the fœtal deer) are clearly and distinctly to be distinguished, and the fœtus is now of the size of a large bean or nutmeg; its occiput is prominent, as in the chick, but its eyes are smaller; the mouth extends from ear to ear, the cheek and lips, as consisting of membranous parts, being perfected at a very late period. In the fœtuses of all animals, indeed, that of man inclusive, the oral aperture without lips or cheeks is seen stretching from ear to ear; and this is the reason, unless I much mistake, why so many are born with the upper lip divided as it is in the hare and camel, whence the common name of *hare-lip* for the deformity. In the development of the human fœtus the upper lip only coalesces in the middle line at a very late period. (Harvey, 1651, pp. 487-488).

Thus, without the aid of the microscope, and long before the exact organogenetic processes were worked out, Harvey saw the possible results of retardation of these processes and laid down the great and eventually fruitful principle of "developmental arrest" as a cause of malformation.

Obviously, however, this theory even when fully developed in the nineteenth century still left in doubt the cause of the developmental arrest.

Neither Harvey nor his immediate successors in England and on the Continent did much to develop the notion; and it was only about 1770 that von Haller and Wolff extended the idea of arrested development to explain *ectopia cordis* and exomphalos; and toward the end of the eighteenth century the idea was extended until it included not only all the monstrosities by defect of formation, but also the double terata. In the nineteenth century the theory was applied even more widely, for during this period knowledge of early human development and of comparative vertebrate anatomy was enormously extended. Hare-lip, cleft-palate, *spina bifida*, exomphalos, *ectopia cordis* and the like appeared to be so easily and evidently explicable as arrested development that they assured for the theory a permanent place in teratogenesis.

Of course the term "arrested development" may cover a great number of phenomena. And, indeed, we can at first agree that in an intermediate sense at any rate, simple arrest of embryonic development or growth may serve to account for many monstrosities and malformations.

Nevertheless, there were many conditions which could not be explained on the theory of developmental arrest; for it was not always possible to point to a specific embryological stage in explanation of an anomaly. And Meckel in 1812 discussed in detail the various arrested developments and pointed out that some of those which occurred in the human subject appeared to represent conditions which were to be found in the lower animals—the idea that the parallel between phylogeny and ontogeny was helpful in explaining malformations which did not resemble any stage in the development of the human embryo, such as the distinct tail due to supernumerary coccygeal vertebræ, the so-called transposition defects as, for example, of the aortic arches *et cetera* and even such abnormalities as those of *sympus dipus*.

But many conditions were not capable of an easy explanation on either embryological or phylogenetic lines other than by a vague suggestion of some very early defect: for example, Meckel himself, in the case of sympodia, expressed the view that "this class of monstrosity was due to an original malformation of the germ", and he explained sympodia and other monstrosities as products of "a formative activity taking a course contrary to the usual operation of its own laws". This is a vague hypothesis, but it is evident that teratologists were being driven to look beyond the usually accepted theories of causation of terata.

It would merely add to the length of my discourse without increasing its value were I to enumerate the embryologists who from time to time throughout the nineteenth century found themselves driven to look for the causative factor in a very early stage and inherent in the fertilized ovum. But it could not be until scientists elucidated the cellular origin of the ovum and spermatozoon (1827, 1841), the unicellularity of these forms (1861), the cell lineage in zygote development (1878) and the details of early development of the embryo (1874 onwards) that much further advance could be made.

The situation at the end of the nineteenth century is summed up by Ballantyne (1902-1904) who, himself inclined to regard abnormality and disease of the amnion as one of the principal causes of congenital anomalies, nevertheless saw that the occurrence of twins, of double monsters, of malformations by excess and of such forms as sympodia, and the hereditary transmission of special malformations from parent to child, could not be reasonably or satisfactorily explained on the basis of amniotic pressure or nutritional defects or developmental arrest; but that there seemed to be no other reasonable explanation of the occurrence of phenomena such as these than that "either in the spermatozoon or in the ovum there was a teratogenic something which determined the abnormal development of the embryo".

Experimental Teratogeny Prior to the Twentieth Century.

From the time of Aristotle onwards, with a long gap during the greater part of the Dark and Middle Ages, we find examples of scientists studying the development of animals, mainly of the chick. But the deliberate study of

the production of abnormalities by interference with the process of artificial incubation is a much later phenomenon: necessarily, the study of teratogenesis was for the most workers merely a by-product of the study of normal development (Ballantyne, 1902-1904; Needham, 1934).

As we have already seen, Aristotle examined developing chicks, derived some considerable knowledge of early monstrous forms and formulated theories of their formation. Amongst the Renaissance biologists were several who made observations on the developing hen's egg; and coming to modern times we find increasing records of the discovery of monstrous forms in the developing chick.

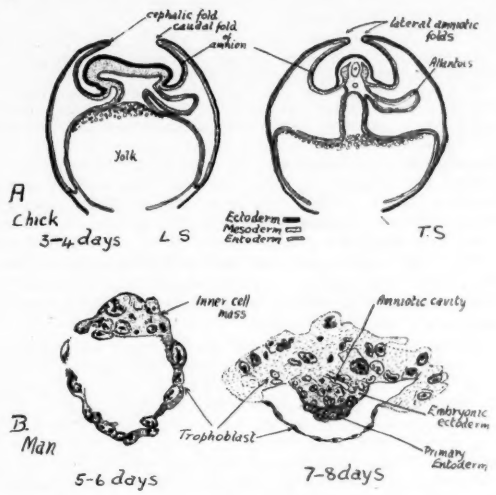

FIGURE IV.

Contrasting development of amnion in chick and man. A. Chick—to show how chick amnion develops by upgrowth and concrescence of four folds. B. Man—to show how amnion develops directly within the inner cell mass. (Based on Hertig and Rock material.)

It was from the partial failure of the attempts at artificial incubation to secure normal chicks that the science of experimental teratogeny took its first origins, for it was often found that many of the chickens thus artificially incubated were deformed. By the beginning of the nineteenth century a great mass of literature had developed on the subject; and it is clear that by that time the artificial incubation of eggs was fairly widely practised, with more or less success, and the frequent teratological results were well known. But it appears that Étienne Geoffrey Saint-Hilaire should be given honour for having in the 1820's first conceived and carried out the idea of turning these experiments to account in the investigation of monstrosities and malformations (I. G. Saint-Hilaire, 1836), for he adopted artificial incubation with the object of producing anomalies at will in the chick by disturbing development in different ways during the early days of incubation (from third day onwards). Various physical agencies were used, and a relatively considerable number of anomalies, both simple and complex, were produced.

These experiments were repeated and extended by the younger (I. G.) Saint-Hilaire in 1831, showing that interference prior to the third day got either no chicks at all or only dwarf ones, but no monstrosities. He came to the conclusion that monstrosities were principally caused by disturbing conditions acting when certain organs of the embryo were developing—an early suggestion of the concept of the "critical period" which was developed fully by Stockard (1920-1921) and which is being used today to explain the development of certain malformations (Ingalls, 1947; Swan, 1949). Here appeared to be a clear demonstration that a change in the physical conditions which determine development may modify the development itself, and evidence against the views of Wolff and Meckel that anomalies arise only from a virtuality placed in the germ before or at the time of fecundation.

During the nineteenth century the chick experiments of the Saint-Hilaires were repeated with or without alteration by many workers, and extended to fish ova (such as pike and trout).

In the second half of the nineteenth century one observer stood out supreme in the field of artificial teratogeny—Camille Dareste, who between 1855 and 1891 carried out and published the results of an enormous amount of experimental work. Working on the chick embryo Dareste soon discovered that the various agents which he used to produce disturbances in embryogenesis all led to the appearance of the same monstrous forms; there was no relation between the nature of the teratogenic cause and the kind of teratological result. Consequently he used almost solely variations of temperature as the teratogenic agent. From his work Dareste was able to draw many important conclusions, which are summarized fully by Ballantyne (1902-1904). He concluded that teratogeny was always the consequence of a modification of the embryonic environment—an overstatement of his legitimate deductions; and he decided against the nosological theory. He laid great stress upon arrest of development as the explanation of almost all malformations of the single embryo. Further, what is of some interest in relation to the specimen I first studied is that he described the arrested development of the amnion, which he thought to be the primary fact of most embryonic monstrosities, and explained how sympodia arose from arrest of the caudal fold of the amnion with compression of the inferior extremities.

A conclusion of great value that followed upon the whole research was the similarity of the monstrosities met with in the chick and those found in the mammalia and especially in the human subject. And Dareste hoped that human teratology might be elucidated by the light of his experimental teratogenesis.

Needless to say many criticisms can be made of his conclusions, both particular and general. Particularly we cannot accept the idea of amnion defect in the chick as being analogous with any such condition in the human, for the formation of the avian amnion is very different from that of the mammalian one (Figure IV). We cannot very well criticize Dareste for not realizing the possibilities of genetically controlled deviations. Again, obvious difficulties in the way of complete acceptance of his views lie in the nature of the teratogenic agents employed and in the transfer of findings from avian to mammalian forms.

About 1894 Charles Féré began his series of observations on chick embryos, using all the old methods, but also bringing the whole subject into line with general pathology by introducing the use of a great variety of chemical substances. He found that, generally, the agents determining anomalies of development produce at the same time a marked retardation of growth and suggested that the anomaly is in relation with the retardation of growth. Rejecting the amnion theory of Dareste as in conflict with his experimental findings (as indeed it was with some of Dareste's own findings), he appears to suggest a change in nutrition as the means by which ontogenesis is arrested and malformations are produced.

III. TERATOGENIC THEORY IN THE TWENTIETH CENTURY.

Although quite obviously there is a continuity of investigation between the nineteenth and twentieth centuries, it seems convenient to treat the last half-century as a separate period, not because of the sudden widespread development of new techniques nor because of any sudden radical development in teratogenic theory, but mainly because the year 1900 saw the rediscovery of Mendel's laws. This event was of importance not only in itself but also in the fact that it gave a new value to concepts and techniques which had been developing during the latter part of the nineteenth century, such as statistical genetics, experimental embryology and the like, and a new basis for the analysis of clinically observed inherited anomalies of

structure and function, which was soon manifested in the work of Garrod, Farabee, Drinkwater and many others. However, apart from genetics, the twentieth century saw the remarkable experimental teratogenic studies of Stockard on the fish and the extension of such work to mammals by Hale and by Warkany and his co-workers; in this period also the collection and refined study of embryological material has been forwarded by workers such as Mall and Streeter to the stage where the beautiful Hertig and Rock material has revolutionized our knowledge of the early development of man (see Figure IV, B); the collection and study of clinical material has become more systematic and complete, as illustrated in such work as that of Fogh-Andersen, Penrose, Julia Bell, Murphy, Birch-Jensen and others; and, further, during the last decade Gregg's remarkable observations on the congenital anomalies consequent on maternal rubella during pregnancy began to bridge the gap between the experimentally produced and the naturally occurring phenomenon.

In this section on the theories of the twentieth century I have divided the material rather loosely between the environmental and the genetic. But the division is one of convenience, for a good deal of the discussion under the heading of environmental could just as rightly have been placed under that of genetic, as, for example, the section on "Pre-natal death: enviromental or germinal?"; and within each of the sections there will obviously be some overlapping of material.

A. ENVIRONMENTAL THEORIES.

Under the general heading of environmental theories I shall examine attempts by embryologists and pathologists, experimental scientists and clinicians to determine the importance of the "environment" as a factor in the production of congenital abnormalities. Here the word environment is used in a very general way to include all factors other than embryonic which could affect the development of the zygote. Strictly speaking this should include everything outside the chorion; but some of the theories now to be considered deal with structures which belong to the zygote but not to the embryo proper, for example, the amnion. However, convenience demands some such arrangement as here adopted.

I shall deal first with a legacy of the nineteenth century —the theory of the mechanical action of the amnion or its adhesions, and of the umbilical cord as teratogenic agents.

Mechanical Factors—Umbilical Cord, Amniotic Bands and Adhesions.

We have already seen the importance attached by many nineteenth century workers to abnormality and disease of the amnion and umbilical cord as teratogenic factors, and also the objections raised to such theories by Meckel, Gatty and others. It remains to see how these theories have fared in the last half-century.

Although we find evidence at various times during this period of the acceptance of these ideas, the theories of amniotic adhesions and bands and of the umbilical cord as causes of congenital abnormalities especially of the limbs (including "intrauterine amputations") but also of the head (and brain) and body wall, would seem to have been disposed of partly by Mall's (1908) analysis of the factors involved and mainly and finally by Streeter's (1930) detailed study of the problem.

Mall (1908) divided the "spontaneous amputation" cases into (*a*) those in which there is an atrophic or rudimentary hand or foot attached, in which the cause was possibly "germinal", as in many other abnormalities of the limbs; and (*b*) those in which there appeared to be an actual amputation, for which Mall said he could give no satisfactory explanation, but for which he could not accept the "irrational" theory of amputation by the cord.

He also dealt with those monsters in which the "malformed part is tied by means of bands of tissue either to the amnion or to adjacent parts of the body of the fœtus", and in which the deformity had been thought to be due to the primary action of the bands and adhesions. Rejecting this explanation, he claimed that "it is highly probable that amniotic bands and the like are secondary in their formation and have nothing whatever to do with the production of monsters"; pointing out that deformities of the extremities are common enough but amniotic bands rare and, when present, often attached to the body of the embryo and not to the deformed extremity; that many abnormalities were simply cases of "arrest of development" of some part of the embryo; that hydramnios is usually present (probably incompatible with adhesions); and that all kinds of monsters may be produced in lower animals, including amphibia—which have no amnion.

In 1930 G. L. Streeter published his paper on "Focal Deficiencies in Fetal Tissues and their Relation to Intrauterine Amputation", in which, as a result of very careful studies, including radiological and histological, he established conclusively that:

> . . . no evidence has been found that intrauterine amputation is due to amniotic bands or adhesions or other mechanical constriction. Amniotic bands do exist and are sometimes associated with malformations, but where this occurs the two participate in the same disturbance and the latter are not mechanically produced by the former.

The anomalies discussed by Streeter (1930) include apparent amputation of body parts by the umbilical cord; amniotic bands and adhesions and typical "amniotic cords"; fibrous "bracelet" on wrist or ankle; skeletal defects and agenesis of the soft parts simulating intrauterine amputation; and intrauterine amputation proper.

He rejects the theory that body parts can be amputated by cord pressure producing a circulatory defect in the part distal to the cord constriction.

From a consideration of the development of the amnion and embryonic disc, Streeter shows that such conditions as, for example, anencephaly combined with an amniotic cord extending from the cephalic abnormality to the amnion proper, are to be interpreted as defective developments arising at a very early stage—at the time when the amnion is being formed and the embryonic disc differentiated in immediate relation to each other. Such amniotic cords and bands are not adhesions or inflammatory products, but are anomalous developmental structures and present from the outset.

Conditions simulating spontaneous intrauterine amputation occur, which are in fact examples of simple skeletal agenesis and of agenesis of the soft parts, generally in varying combinations. These are generally confined to one extremity, show no open or healing wounds and no masses or strands of degenerate fœtal tissue such as are characteristic of true amputations. Further, where the skin is present over the distal parts, it generally shows the ridge configuration typical of the digits.

Finally, Streeter sets out what might be called the natural history of the true spontaneous intrauterine amputations, from cases seen in the first half of pregnancy, through later fœtal stages, infancy, youth, and adulthood, in which the principal lesion (histologically demonstrated) in the limbs is an imperfect histogenesis, of varying degree of development, mainly in the mesenchymal tissues and particularly in the subcutaneous connective tissues, and sometimes involving bone and muscle.

In spite of Streeter's work, we still find the explanation of fœtal abnormalities as caused by anomalies of the amnion or compression by the cord put forward, as, for example, in Johns's (1946) citation of Ballantyne's (1902-1904) theories of adhesiveness and pressure as an explanation of the ætiology of a case of congenital gastroschisis and in his statement that "Students of antenatal pathology are agreed that amniotic displacement is the most frequent factor in the production of monstrosities". Such may have been the case in the earlier decades of this century; it is hardly the case today.

Streeter's work removed a considerable number of fœtal abnormalities from the field of mechanically caused anomalies and put them back at an earlier stage—some constitutional defect of a "germinal" nature.[1]

[1] It should be noted, however, that Birch-Jensen in his "Congenital Deformities of the Upper Extremities" (1949) merely records Streeter's views among many others.

Stockard's Theory of Developmental Arrest Due to Altered Environment (Mainly Oxygen Changes).

In 1920-1921 Stockard reported the results of his remarkable experiments on the development of *Fundulus heteroclitus* (the common marine minnow). By variations in the temperature and chemical content (especially oxygen) of the medium in which the eggs were developing, he was able to produce many types of abnormality, simple and complex, double as well as single (Stockard, 1920-1921). So widespread has been the acceptance of Stockard's theories and so frequent the references to them, as, for example, by Ingalls (1947) and Swan (1949), that it seems desirable to state them fairly fully.

Stockard observed that in the minnow all types of monster may be caused by one and the same experimental treatment; that any one type may be produced by a great number of different experimental treatments if applied at the same phase of development; that the same disturbing factor, applied at different phases of development, produces different defects; that is, the type of defect produced by any experimental technique depends on the stage at which the environmental change is induced. From these general observations, here too briefly summarized, Stockard deduced a conception of very great theoretical importance. Not all parts of the embryo develop at the same rate, for different parts and organ-systems develop rapidly at different stages of the whole organism's growth; that is, at different times there are marked inequalities in the rate of cellular proliferation in different parts of the embryo and in the different organ-systems. Further, "the development and growth of organs in the single individual are inter-related. When one organ or one component has a higher rate than another, it develops at this rate for a limited time and tends to inhibit development on the part of other organs". And for any particular organ or organ-system there appears to be a "critical moment" in which any marked interference with the rate of developmental processes will be followed by most disastrous results.

Now, a cardinal feature of Stockard's theory is that the effect which all teratogenically effective treatments have is that they tend primarily to lower the rate of development, that is, all disturbing agents have in common the power of slowing or stopping growth. According to his conception the inhibiting agent need not act for any great length of time, for the site of accelerated cellular activity shifts as development proceeds; but if the inhibiting effect operates while a particular organ is in that "transient critical stage of differentiation", that organ will never subsequently be able to undergo the changes which should have taken place at the "critical moment". Further, Stockard held that there were stages of apparent indifference to a stop in or slowing of development—stages when no unusually great rates of local proliferation are present. At such stages the usual teratogenic agents would have little or no effect.

It would appear that he believed that the effect on developmental rate was mainly an oxygen effect—either a direct cutting-off of oxygen, as in some of his experiments; or, in the temperature-lowering experiments, an indirect effect produced by the resulting reduction in the rate of oxidation.

Another sweeping generalization Stockard made was that monsters by defect, normals, monsters by excess and, finally, identical twins are all part of a continuous series: "All monsters are the result of the same cause, and the type of monster depends upon the time at which the cause was in operation."

On whether his results can be applied to mammals Stockard writes:

> While in mammals the temperature changes are eliminated by the internal mode of development, the one great danger to normal development still not completely controlled is the chance of a low oxygen supply brought about by a delayed or poor implantation of the placenta. The great majority of monsters in mammals are very probably due to an insufficient oxygen supply during development, and this results as a rule from faulty placentation.

(Compare Mall's theories, later.) However, there are several difficulties in the way of fully accepting Stockard's theory. In the first place we cannot accept the transfer of his argument from fish to mammal, for the developmental processes are very different in the two cases; nor can we, in view of what is now known from experimental and other observations, agree that in mammals "the one great danger to normal development still not completely controlled is the chance of a low oxygen supply". Again, there is the difficulty of known hereditary abnormalities. In his introductory pages, Stockard writes (page 117): "I have claimed that all types of monsters *not of hereditary origin*[1] are to be interpreted simply as developmental arrests." The difficulty here is that Stockard (as also Mall) does not make clear how we are to tell what monsters are of hereditary origin. Finally, on the question of whether "developmental arrest" is the mechanism by which abnormalities are produced, Patten (1947) strikes a warning note, pointing out that in certain developmental defects of the nervous system and of the heart,

> . . . the abnormal conditions which appear are far more varied than can possibly be accounted for on the basis of a mere cessation or retardation somewhere along the course of normal development. There are certainly many anomalies which can most readily be so explained, but there are others which are due to such widely divergent processes as growth which has gone too far, resorption which has gone too far, resorption which has not gone far enough, or growth fairly normal in amount but abnormal in location. Such radical differences in the immediate mechanisms concerned should give us pause in considering any "blanket explanation" of congenital defects.

Maternal Nutritional Factors—Experimental.

As Landtman points out, it has long been known that fœtal development *in utero* is particularly related to the nutritional condition of the mother; in the last world war an unusually high incidence of premature births associated with maternal starvation during pregnancy was reported; and some authors have observed a relatively high incidence of dietary deficiency during pregnancy among mothers of malformed children (Landtman, 1948).

This problem has been investigated in mammals, and that specific insufficiencies in maternal nutrition may produce congenital defects in the offspring has been clearly shown by Hale (in pigs), and much more extensively by Warkany and his co-workers (in rats). All this work was done with adequate controls and without direct intervention on the embryo or its environment; and in both series genetic factors were excluded and the dietary factor was confirmed.

Hale (1933, 1935) from sows of known stocks, maintained prior to and during the first thirty days of pregnancy on a diet deficient in vitamin *A* and possibly in other nutritional factors, obtained pigs showing severely malformed eyes (anophthalmos and microphthalmos) harelip, cleft palate, ectopic kidneys, subcutaneous cysts, and accessory external ears.

In a brilliant series of experimental studies on rats during the last decade Warkany and his co-workers showed that a remarkable assemblage of fœtal abnormalities may be produced in the offspring by a vitamin-deficient maternal diet—multiple skeletal abnormalities, ocular defects, a great variety of genito-urinary tract malformations, diaphragmatic defects, and aortic arch and cardiac abnormalities (Warkany and Nelson, 1940; Warkany and Schraffenberger, 1944, 1946; Warkany and Roth, 1948; Wilson and Warkany, 1948, 1949). One remarkable feature of the findings is the variations occurring in the incidence of abnormalities in litters from the same mothers, both as between litters and within litters—a condition similar to that seen in certain genetically controlled anomalies.

However, it does not follow that these experimental results obtained in other mammals necessarily apply to man. In the first place, in the experiments described the deprivation of the material under study was as complete as it was possible to make it—a condition that can rarely

[1] The italics are mine. M.F.H.

be obtained in human cases. In fact, in the second place, Landtman (1948) cites the work of Brzezinski and others as showing that there was no observable increased incidence of malformations in the children of 326 mothers who had suffered from riboflavin deficiency during pregnancy.

Maternal Environment.

Clinical Study of Teratogenic Effects of Infectious Diseases.

It has long been recognized that infectious diseases affecting the mother during pregnancy may occasionally be transmitted to the fœtus as a disease, as, for example, fœtal variola, malaria, yellow fever and relapsing fever.

Again, severe infections during pregnancy are likely to cause the death of the fœtus: in the severe influenza epidemic of 1918, from 30% to 50% of mothers affected

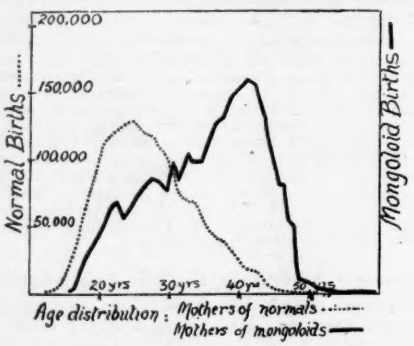

FIGURE V.

Bleyer's analysis of 2822 cases of mongoloids showing age distribution of mothers of mongoloids as compared with that of mothers of normal children.

during pregnancy lost their babies as a result of abortions, still-births, or neo-natal deaths. Probably most of these disasters were due to the direct effect of the actual disease on the fœtus or the mother; but it is possible that some of the cases were examples of an indirect effect of the disease on the maternal-fœtal relationship, as, for example, by so disordering embryonic development as to produce congenital abnormalities interfering with the viability of the embryo (Landtman, 1948).

Further, it has been claimed that maternal syphilis and maternal tuberculosis may be causally related to certain congenital malformations in the fœtus (distinct in the case of the first condition from the syndrome of "congenital syphilis") (Landtman, 1948; Murphy, 1947).

Rubella. It is hardly necessary to remind an Australian medical audience that during the last decade, since the pioneer work of Gregg (1941), a considerable amount of evidence has accumulated that an attack of maternal rubella, even of a mild degree, during the first three months of pregnancy may produce grave malformations. Here we have a supposedly benign disease, previously considered too slight in its effects on the mother to cause any influence on fœtal health, suddenly with Gregg's work assuming a more serious significance.

Gregg's study opened up an entirely new way of thinking about non-hereditary congenital anomalies; and since the first reports by Gregg (1941 *et cetera*) and Swan (1943 *et cetera*), of which a full bibliography is given by Swan (1949), a large number of workers both in Australia and in other countries have reported a similar relationship. The accumulation of evidence was accompanied by an increase in the number of defects thought to be directly attributable to pregnancy maternal rubella to include eye defects (mainly but not exclusively cataract), deafness, cardiac lesions, microcephaly, mental retardation, dental defects, hydrocephaly, mongolism, and several other major defects. Further, there is suggestive evidence that a certain proportion of mothers infected with rubella in the early months of pregnancy suffer abortions, miscarriages or still-births, maybe through the development of a congenital abnormality interfering greatly with the viability of the embryo (or fœtus) (Patrick, 1948; Swan, 1948, 1949).

Although some problems still remain to be settled, it is the considered opinion of such workers as Murphy (1947), Landtman (1948), Swan (1949), Ingalls (1950) and many others that there can be no doubt, from the formidable array of statistics accumulated to date, that maternal rubella is in some way causally related to congenital anomalies in infants. There are still several important difficulties to be cleared up, but these have been recognized and do not appear to be beyond solution.[1]

One of the problems arising from these studies is the actual risk involved to the fœtus if the mother contracts rubella during pregnancy. This is difficult to assess, and widely varying estimates have been given by different workers (Swan, 1949; Gruenwald, 1947; Landtman, 1948; Patrick, 1948). But there appears to be no doubt that the risk for the first four months of pregnancy cannot be set much below 30%; some would set it much higher.

Now, as you all recognize, this question is not only of academic and statistical importance, for the serious nature of many of the defects *plus* the high incidence of defects attributed to pregnancy rubella has led to suggestions for prophylaxis including therapeutic abortion of women developing rubella in the first three months of pregnancy (for example, Swan, 1949).

Into the question of whether infectious diseases other than rubella during pregnancy may cause similar congenital defects I shall not enter here, other than to say that there is some suggestive evidence that such may be the case, for example with maternal measles during pregnancy (Albaugh, 1945), with chicken-pox (Murphy, 1947), and with influenza (Landtman, 1948). The matter is discussed by Aycock and Ingalls (1946), Murphy (1947), Landtman (1948), Swan (1949), and others. This question merits and is receiving fuller investigation and there is no reason for expecting to find that rubella is the only teratogenic maternal disease. For, as Ingalls (1950) points out: "Experimental and clinical facts assembled to date indicate that a single agent may cause multiple defects of differentiating tissues; conversely, that a particular defect may be caused by multiple agents acting during a particular stage of differentiation. The two principles give some indication of the nature of the epidemiologic problem remaining to be investigated."

Other Aspects of Maternal Environment.

We can briefly mention some other conditions the causal factors in which, environmental or genetic, are not yet elucidated. In endemic cretinism there are associated with the physical stigmata, mental deficiency and, in the same endemic areas, deaf-mutism. In these cases there are not

[1] Some of the difficulties in the problem have been (i) the reliability of the diagnosis of rubella; (ii) the methods of collecting the evidence retrospectively from mothers of malformed children; (iii) the difficulty of making prospective investigations; (iv) the variation in the damaging effects of various epidemics; (v) the variation in the damaging effects of any one epidemic; (vi) the association of rubella late in pregnancy with similar congenital defects (here the same mechanism, for example, developmental arrest during the "critical moment", can scarcely be invoked as for the early stages of pregnancy); (vii) the occurrence of congenital deformities following pre-conception rubella; (viii) the absence of congenital defects in many cases following rubella in pregnancy; (ix) the occurrence of congenital malformations similar to those described in association with rubella, in the apparent absence of infection during pregnancy; (x) the lack of complete family histories—of importance in cases of deaf-mutism attributed to pregnancy rubella, but which may be genetically determined; (xi) the extraordinary unilaterality of some lesions, for example, one eye may be gravely malformed while the other remains seemingly unaffected; (xii) the experimental elucidation of the mechanism of the production of the anomalies—whether the fœtus itself is infected, with the virus acting directly on embryonic and fœtal tissues, as suggested by Hamburger and Habel (1947); or whether the primary changes are in the maternal organism, and the embryonic and fœtal changes are secondary to a disordered maternal metabolism, as suggested by Gillman and his co-workers (1948).

only environmental factors to be considered, but also intrinsic ones, such as an hereditary inability to use iodine (Gruenwald, 1947). Again, a fairly high incidence of developmental anomalies is reported in the children of diabetic mothers (compare Eastman in Rock and Hertig, 1948; and Dods, 1948, page 782).

Mongolism is another common congenital condition not yet elucidated. You will all be familiar with the commonly expressed view that it is determined by the relatively advanced age of the mother. Now this question of maternal age in relation to congenital defect is an interesting one. In general it has long been believed that there is a greater liability of older mothers to bear malformed children, a belief supported by such investigations as those of Murphy (1947) and Landtman (1948). And this is particularly marked in mongolism—women who become pregnant in the late period of their reproductive years have a chance of several *per centum* of having an affected child, while only a fraction of 1% among the births of younger mothers is affected. But the question is not a simple one, as examination of Figure V will show. Although Bleyer's curve (Figure V) clearly shows an association between mongolism and relatively advanced maternal age, and although this alone is strong evidence of a maternal factor related to advanced age operating in the causation of the condition, nevertheless, the long age-span covered by the curve and the several irregularities and eminences at other ages than forty-one years, demonstrate that additional factors must operate. Ingalls (1947, 1950), suggests that the condition appears to originate during a "critical period" between the sixth and ninth weeks of fœtal life and deduces that a cause acting at or before that time should be sought for. He claims that there is ample evidence of a significantly increased frequency of ante-natal disturbances (including uterine hæmorrhage, threatened abortion associated with mechanical disorders of the uterus, and certain intercurrent infections) observed at the "critical period" among mothers who gave birth to mongoloid babies as compared with mothers of the general population. We cannot now discuss the merits of Ingall's theory, which specifically excludes hereditary factors; indeed, it is by no means certain that mongolism has not a genetic basis (Southwick, 1939; Rosanoff, cited by Stern, 1950), and Stern considers that the data on mongolism in twins, homozygous and heterozygous, make it probable that there is a genetic basis, but one of considerable complexity.

Whatever solution is finally reached on the problem of the ætiology of mongolism, it will have to take cognizance of the factors of maternal age, the maternal environmental conditions (general and uterine), the embryonic possibilities, and the special features of the incidence of mongolism in homozygous as compared with heterozygous twins.

The Effects of X-Ray and Radium Irradiation.

Theoretically, congenital abnormalities of two types might be produced by radiation damage: (*a*) by direct action on the developing tissues of an embryo; (*b*) by the induction of genetic changes, transmitted through the gametes, the effects of which will appear only in subsequent generations. Consequently I shall consider here the genetic as well as the environmental effects.

Direct Somatic Effect.

As early as 1907 Hippel and Pagenstacher had observed that X-ray irradiation of pregnant animals could cause malformation in the offspring. During the last fifteen years, mammalian experiments of increasing precision (Job, Liebold and Fitzmaurice, 1935; Kaven, 1939, cited by Wilson and Karr, 1951; Warkany and Schraffenberger, 1947; Wilson and Karr, 1951) have adequately demonstrated that radiations, especially X rays, administered at certain dosage levels during embryonic life may alter the normal course of development as evidenced by the presence of grossly visible anomalies at the time of birth; that the degree of damage depends partly on the time of irradiation, partly on the dosage; that doses of radiation higher than those which cause maldevelopment result in the intra-uterine death of a majority or all of the animals; that the effects, as we would expect from experimental work with other teratogenic agents, show definite variations (probably the specific reaction of the individual genotype of the embryo in question). And this evidence would suggest strongly that therapeutic X-ray and radium irradiation of the pregnant human pelvis is also very likely to produce general retardation and malformations of the fœtus, and even pre-natal death with abortion.

This expectation appears to be borne out by clinical observations. It has long been well known that damage to the fœtus by therapeutic irradiation of both types may result in microcephaly (commonly), hydrocephalus, microphthalmia and other malformations (such as *spina bifida*, deformities of extremities *et cetera* (Murphy and Goldstein, 1929; Gruenwald, 1947; Murphy, 1947, with full reference list). It appears to be well established that a definite proportion of pregnancies subjected to therapeutic maternal irradiation end in abortions (Murphy and Goldstein, 1929). Murphy (1947) reports that of the children born (at term) to 106 women who had been exposed to X-ray and radium irradiation during pregnancy for various reasons, 37% manifested mental or physical abnormalities which could not be attributed to any cause other than irradiation. Of the affected children 70% suffered severe disturbances of the central nervous system. Murphy, however, could not assess the relation between the amount of radiation employed and the type or severity of the defect exhibited in the offspring.

The above evidence, experimental and clinical, makes obvious the need for preventing the irradiation of the fœtus. To secure this end, Murphy (1929) suggested that in women of the child-bearing age each therapeutic irradiation of the pelvic region should be preceded by a diagnostic curettage. It does not appear that diagnostic doses as used for skiagrams are harmful to the fœtus, although this is by no means certain—especially with repeated skiagrams; and fluoroscopy should be used with the greatest caution (Gruenwald, 1947; Birch-Jensen, 1949).

Induction of Genetic Changes by X Rays et cetera.

We now deal with a quite different matter—"the more problematic effect of radiations on the genotype, producing mutations which determine hereditary malformations in the offspring". Present opinion of medical scientists would appear to be reflected in the statement of Gruenwald (1947) that the occurrence of alterations in the genotype due to radiation-induced mutations in the gametes and the causation of malformations by these in man, has not yet been established (and compare Murphy, 1947). However, the matter is not quite so simple as such remarks would suggest.

A great deal of refined experimental work has fully established that mutations can be induced by the use of X rays on both invertebrate and vertebrate (including mammalian) forms.

The possibility of radiation damage to genetic material has been very lucidly discussed in a recent paper by H. J. Muller (1950). It is of basic importance to realize that most mutations lead to abnormalities. The majority of induced mutations are lethal; another large group of mutants shows a greatly lowered viability as compared to normal; and hardly any mutant has a survival rate as high as the normal forms. But, although the great majority of mutant genes are harmful in some way, their damaging effects are seldom obvious. In the first place, their manifestations are much oftener of a physiological rather than a morphological nature; and, in the second place, a given mutant gene is usually received by an individual from only one of his parents, and, although most mutant genes do possess a significant but slight degree of dominance, they would, by ordinary standards, be termed recessive. Now, the possibility of the homozygous condition arising will increase with the rate of production of mutant genes (putting aside the fact that recessive mutants may produce early death or abortion of the embryo). The reduction of viability caused by mutant genes is in the end directly proportional to the frequency with which mutants originate. It is, therefore, evident that any agent or condition which affects mutation frequency must be of prime

importance for human well-being. High-energy radiation capable of causing ionization induces gene mutations similar to those occurring naturally, and to a similar extent harmful. The frequency of these mutations is directly proportional to the total dose received, no matter whether treatment is concentrated, attenuated, or divided into fractions separated by great intervals. There is no dose too small to show some effectiveness proportional to its size, and there is no recovery from the mutational effect even though the reproductive organs may regain apparently normal function. Thus there would be a cumulative effect of induced gene mutations. Nevertheless, because of the inconspicuous nature of most mutational effects and the fact that many generations usually elapse before a mutation results in genetic death, it is not to be expected that the exposure of any one generation, even to the maximum dose it can tolerate, will be followed by early demonstrable detrimental effects in the next generation or two; this state of affairs might make men more reckless with radiation agents than if the genetic effects were exerted in a more concentrated and conspicuous form.

Muller concludes his discussion as follows:

> The above considerations show that the indications hitherto commonly used by those dealing with ionizing radiation or radioactive materials as guides for keeping within "safe dosage" limits—namely, the avoidance of reddening of the skin, falling out of hair, change in the blood count, loss of sperm motility *et cetera*—are by no means reliable criteria, and that important damage to the individual himself can result from a repetition of doses far too small to give these more obvious effects. As a result, the total of this surreptitious damage to the exposed population may be very considerable, although probably not comparable, reckoned in number of years of life lost, to the total amount of damage which would be caused to future generations by this one generation's exposure. Paradoxically, it is probably fortunate that this somatic damage to the exposed generation does result. For, when it is realized that the individual himself runs some risk, measures are more likely to be adopted which will protect him better, and in doing so, they will automatically tend to protect the interests of future generations as well.

Pre-Natal Death—Environmental or Germinal?

In the early years of this century there was a widespread belief that pre-natal death is very largely if not entirely due to disease of the maternal tissues. (Compare Ballantyne, 1902-1904; and Robinson, 1921.)

This belief received strong support from Franklin P. Mall, who examined a large number of human specimens (163 pathological embryos collected during 15 years), and published his findings in "A Study of the Causes Underlying the Origin of Human Monsters" (1908). From an examination of the membranes in all cases possible, he came to the conclusion that the membranes of nearly all pathological ova are pathological; that the inflammatory and other changes found in the chorion and uterus are primary, interfering with the attachment of the ovum; that the changes in the embryo and its membranes, due to the inflammatory action in the uterus, are so great that the ovum is either (usually) aborted at an early date or converted into a solid mole which in the course of time is likewise expelled; that pathological embryos and small monsters are generally identical, that is, many of them would have developed into real monsters if they had not been aborted; and, finally that "all monsters are produced by external influences upon normal ova which affect the nutrition of the embryos due to faulty implantation of the ovum whether in a diseased uterus or in the uterine tubes".

Although Mall's work is frequently cited, we cannot accept his broad generalizations. He himself admits that there are "monsters of an hereditary nature", and he also admits that his criteria of division of hereditary and environmental are quite arbitrary. Further, there is strong evidence for the existence of many examples of genetically controlled "arrests of development" and abnormalities involving "more or less destruction of the fœtus"—the very conditions which he claimed were seen in his pathological embryos. Further, Mall stressed that the ova were normal to start with—that an embryo which has reached a comparatively advanced stage of development before it shows any obvious signs of degeneration was originally normal. As Robinson (1921) comments: "Such a position is untenable, for it assumes that a mechanism which shows no obvious signs of defect when it is first put into action is normal, although it may have an invisible structural defect which may result in its breakdown before the end of its normal period of working life is attained."

Another difficulty in Mall's argument, apart from the meagre histological evidence, is that he does not deal with the very real possibility that the defective attachment of the embryo may itself be due to an inherent defect in the embryo; and he gives no clear proof that a diseased uterus or tube causes faulty implantation of the chorion, leading to nutritional impairment and so to changes in the developing embryo. In fact, as will be seen from the following paragraphs, there is sound evidence that in some cases the defectiveness of the zygote is manifest before implantation has begun and certainly while it is in its very earliest stages (Corner, 1920; Carnegie Year Book Number 46, 1946-1947; Robinson, 1921; Rock and Hertig, 1948).

Mall's views, however, did not remain long unchallenged. In 1915 Huber, working with the albino rat, found evidence in abnormal morulæ and gastrulæ that the cause of prenatal death cannot in some cases be attributed to uterine disease (Huber, 1915*a*, cited by Robinson, 1921).

Corner (1920) observed in the pig embryo various degenerative changes and abnormalities of growth, occurring before the age of two weeks, at a time when the blastodermic vesicles are not yet attached to the uterine mucosa. "These specimens taken in conjunction with the larger series reported by Huber (1915*b*) indicate the probable occurrence of exceptions to Mall's rule that all pathological mammalian embryos are due to faulty implantation." From a later report (Carnegie Year Book Number 46, 1946-1947), it appears that Corner has shown that in pigs about 30% of all embryos are abnormal, and that one-third of these are already defective in the phase of segmentation.

In his too little known Struthers Lecture of 1920 Arthur Robinson gave the findings of his studies on the incidence and causation of pre-natal death in mammals, that is, "the death of ripe extruded ova, or of the zygotes formed by the union of such ova with spermatozoa before the termination of the normal period of gestation" (Robinson, 1921). Basing his conclusions on a careful analysis of results in horses (breeding records in a total of nearly 32,000 matings) and in ferrets (breeding records supplemented by detailed macroscopic and microscopic study of deliberately killed pregnant animals—165 matings, 1643 *corpora lutea*, 1246 zygotes), he found for horses a "normal" pre-natal death rate of over 40%, and for ferrets of over 30%.

The work on the ferret is very significant, for Robinson was able by detailed histological studies to show that the largest part of the lost ova died as zygotes, some in the morula stage, some in the blastula stage before and after attachment, and some in later differentiated stages; and further, that degenerating zygotes were found in company with perfectly healthy ones in the same uterine cornu, and that maternal environmental factors could in most cases be excluded. The pre-natal death of the zygotes, therefore, was due simply to an inherent incapacity to live and develop properly under conditions which were quite favourable to immediately adjacent zygotes; and this incapacity was due to a defect in the constitution of the gametes and zygotes.

As to the reaction of the maternal organism: obviously the "abortion" of non-attached zygotes will generally not be noticed; but the pre-natal death of an attached zygote must be followed by absorption or abortion of the dead zygote, and the more complete the attachment the greater the disturbance involved. The reaction depends on the type of pregnancy: in animals with multiple births, the dead zygote is generally dealt with by absorption—otherwise all the zygotes would be extruded; but in long gestational animals, especially those with (usually) single

births, the death of the zygote is usually quickly[1] followed by abortion and this by the speedy reconstitution of the mucosa. In healthy animals "abortions which follow normal pre-natal death are themselves normal, and the changes found in the uterine mucosa in such cases are regressive and useful, and not inflammatory or degenerative", contrary to what was claimed by Mall (1908).

Robinson's conclusion is that a high pre-natal death rate is a normal occurrence in healthy animals placed in a normal environment, but very variable in its incidence in animals of the same group and for individual animals in different matings. From the general high death-rate in several widely different groups of mammals he concludes that there is every reason to believe that it will be found to be not less high in other groups, including man; and that for humans a considerable amount of pre-natal death is normal and usual, and, under ordinary circumstances, cannot be avoided; and consequently a considerable number of abortions are inevitable and normal. From British figures Robinson estimates the human pre-natal mortality rate (unavoidable) at probably about 40%, perhaps more.

Finally, in the now famous Hertig and Rock series of early embryos, ranging from the early cleavage stages to the stage of the well-established embryonic disc, it appears that of the 26 very young embryos naturally conceived, twelve are considered to be abnormal in either trophoblastic or dermal tissue or both, some even lacking the inner cell mass or the embryonic disc (Rock and Hertig, 1948), that is they show some abnormality, often of such a serious nature that it is incompatible with the continuation of the pregnancy (Carnegie Year Book Number 46, 1946-1947).

In a discussion of Rock and Hertig's paper, Carl Huber mentioned an earlier series of twelve early embryos of which five were abnormal, thus confirming the high frequency of abnormality in early embryos. This brings the series to 38 very young embryos, with 17 of them abnormal, that is almost 45%.

With regard to the question of environment as a factor in producing abnormalities and so causing abortion, Rock reported that with one exception in all of their 26 cases the endometrium was normal as far as cytology and staining were concerned. The site of implantation (anterior or posterior uterine) did not seem to make any significant difference to the occurrence of abnormality: of the three non-implanted zygotes, two were definitely abnormal, the third probably so.

The figure of 45% for abnormal human zygotes, although the series is small, is of interest when compared with Robinson's (1921) figures of pre-natal death for the horse (40% *plus*), ferret (30% *plus*) and (estimated) human (40%).

This suggestion, that a fairly high percentage of pre-natal mortality and abnormality is "normal" and unavoidable, and due to other than environmental causes, brings us, naturally, to consider the twentieth century theories of genetically determined congenital abnormalities.

B. GENETIC THEORIES.

Introduction.

There is no need with this audience to give even an outline of the development of modern genetics or any brief statement of the general principles of the science. Modern genetics began in 1900 with the rediscovery of Mendel's laws and of Mendel's work on them, by Correns, de Vries and von Tschermak. The material of genetics was first plants; but soon animals came within its purview, and it was quickly realized by many workers that man was doubtless subject to the newly discovered laws of biological inheritance, but perhaps with some modifications.

Prior to 1900 there had been many observations of the "familial" and hereditary nature of numerous physical traits, anomalies and diseases; but since then a new science of genetics has sprung up including human genetics; and now a great deal is known about the hereditary transmission of many characters and anomalies, functional as well as structural, about "sex-linked" characters, about the origin of new anomalies as mutations, and about the action of genes.

As early as 1902 the clinical observation of inherited anomalies, diseases and tendencies to disease in man was put on a completely new footing by Garrod (1902), who in that year published a short paper in which he put forward the hypothesis that alkaptonuria is determined by a single recessive Mendelian factor, that is, in the modern jargon, by "an autosomal recessive gene substitution". This work showed the possibility of interpreting familial conditions as recessive traits, and it provided the instrument for examining the occurrence of recessive traits "in a species whose matings cannot be regulated by the investigator to meet the more obvious requirements of Mendelian hypothesis"—the collection of data concerning the incidence of first cousin marriages among normal parents of persons exhibiting the recessive trait. Then, in 1905 Farabee, in his study of a pedigree of one type of the skeletal abnormality of brachydactyly of the hand, manifested in five successive generations of an American family group, first demonstrated dominant Mendelian inheritance in man (Farabee, 1905).

During the last-half-century the genetic pattern of many inherited characters, including anomalies of function as well as of structure, has been worked out in increasing detail and accuracy (compare classification in Ford, 1942); the formal genetics of man has been expounded (Haldane, 1948); genetic counselling is now recognized as an important aspect of medical work (Stern, 1950; Penrose, 1950; and Neel, 1951) and the methodology of medical genetics has been briefly stated by Hogben (1950).

I can do no more than mention the great debt of human genetics and, therefore, of medical science to general genetics with its enormous equipment of wide observations and diverse techniques of theoretical and laboratory experimental inquiry, drawing on a long range of organic types, including plants as well as animals. But we must remind ourselves also of what Hogben (1950) calls "the pitfalls which beset the application of principles established by such inquiries without due regard for the uniqueness of man". Some of the difficulties in human genetics are: the lack of experiments and the difficulty of carrying out adequate ones; the relatively large number of chromosomes in man; the extreme heterozygosity of man, making it impossible to establish true-breeding strains; the low fertility and long interval between generations of man; the comparative rareness of intermarriage in human stocks; the difficulty of accurate measurement of most of the characters studied; the belief that the occurrence of any marked congenital abnormality is a stigma on the family, which leads to a reluctance to provide adequate information on pedigrees.

In the earlier part of this century enthusiastic workers, reasoning from findings in other animals, drew rather too far-reaching conclusions about the hereditary nature of differences among human individuals and about the consequences for mankind of the transmission of these differences to future generations. These conclusions were carried far beyond the theoretical stage to actual plans for "eugenic" control of reproduction; and when it became evident that they were based upon a too limited knowledge of the factual basis of man's inheritance, the "eugenic movement" was rather widely discredited.

Nevertheless, human genetics has already made important contributions to practical problems and we may expect its usefulness to increase in the future.

Heredity and Abnormality.

The tendency for certain congenital abnormalities and for certain functional disorders to occur in families was noticed long before the twentieth century, but it was only with the development of the new techniques of genetic analysis that investigators began to understand the various types of inheritance.

[1] Not necessarily the case in human pregnancy (Streeter, 1930, page 5, stating that the dead fœtus is retained for about six weeks in many cases).

Certain malformations and other anomalies, structural and functional, are inherited with a regularity that suggests a dominant character, perhaps dependent on a gene defect which originated as a mutation. Some of the better known conditions determined probably by a single dominant gene include achondroplastic dwarfing, bone fragility and blue sclerotics, brachydactyly, epiloia, juvenile cataract, piebalding, polydactyly, *retinitis pigmentosa* (some forms), "lobster claw" ("an unmistakable dominant", Haldane, 1948), split foot, white forelock, woolly hair (in Europeans), retinoblastoma, Osler's disease (multiple telangiectasia), neurofibromatosis.

Others, again, occur as simple recessives, for example, most cases of albinism, infantile amaurotic idiocy, certain forms of *retinitis pigmentosa*, and so on. In the case of a recessive character the defect might be carried in the germ-plasm of an apparently normal individual (heterozygous) until a mating occurred with another apparently normal person with the same latent defect, with the possibility then of the production of offspring homozygous for the defect.

Further, sex-linkage, partial or full, has been demonstrated for several genes determining various abnormal conditions, such as *retinitis pigmentosa* without deafness, recessive spastic paraplegia; recessive *xeroderma pigmentosum*, hæmophilia (Ford, 1942). Most of the conditions already mentioned are mainly structural, at least at first glance. However, functional abnormalities are well known as both recessive and dominant gene-controlled conditions. Indeed it was in this functional field that Garrod in the earliest years of this century first demonstrated a human trait (alkaptonuria) to be determined by a single autosomal recessive gene substitution, and showed that genic differences between individuals responsible for clinical peculiarities could be detected biochemically (Garrod, 1902). Another functional abnormality of which you will have all heard is congenital stationary night-blindness, a type of grossly defective twilight vision which is inherited as a dominant. There is no need to extend this list.

Serology, again, is a field in which genetics has a very definite place. The four classical blood groups[1] were discovered in 1900-1902 by Landsteiner and his pupils. It was fairly soon realized that the blood groups were inherited, but at first the exact mechanism was not understood. It was only in 1925 that Bernstein showed that the mechanism of inheritance depends upon a series of three allelic genes, that is, three genes which can occupy the same locus on a certain chromosome. In dealing with the long-recognized danger arising from the transfusion of incompatible donor's corpuscles into the recipient's serum, if prior cross-matching is not carried out, genetical knowledge is, of course, helpful but not absolutely essential. But the incompatibility of a fœtus with its mother can be predicted on genetical grounds and appropriate treatment planned before it is possible to examine the fœtal blood. The association of fœtal disease with rhesus incompatibility, first recognized by Levine, Katzin and Burnham in 1941, is "the most dramatic and convincing demonstration of the use of genetics in medicine" (Penrose, 1950).[2] However, its importance is well known to you all.

Now there are many malformations and anomalies in which heredity would seem to be implicated, but in a manner not always easy to follow. Such defects, for example, as cleft lip and cleft palate appear, on the basis of present evidence, to be inherited in the manner of a Mendelian recessive character: an hereditary disposition would be the essential ætiological factor (Fogh-Andersen, 1942). Of course the question of the inheritance of genes, either recessive or dominant, for functional or structural anomalies, is in many cases not a simple one. And in the case of man, as explained earlier, there are special difficulties.

Although we tend to assume that "dominance" and "recessiveness" are relatively simple conditions, that is far from being the case, for any particular gene can only act in an environment, part of which is provided by the other genes and gene complexes. A well recognized concept is that of the "modifying genes" which are believed to enhance or diminish the effects of other (main) genes which determine the more conspicuous characters and whose presence can be detected only if these other (main) genes are producing their effect. As early as 1907 Cuénot investigated the intensifying and diluting genes which influence the effect of other colour factors in mice; and later a conclusive demonstration of these "specific modifiers" was possible in *Drosophila* by linkage tests for the modification of "eosin" eye colour. An example of a modifying gene (allele) in man is provided by the studies of Mohr and Wriedt (1919) of a "new type of hereditary brachyphalangy" in a Norwegian family traced without a break through six generations. The character, dominant, and not sex-linked, is found in the one family in two clearly different forms of expression, one of very mild degree in which only a careful inspection of the hands (including radiological) reveals a slightly expressed brachyphalangy (the *B* type of Mohr and Wriedt); and another (the *B*! type) in which the second finger is shortened strikingly. This tendency suggests, by analogy with the work mentioned above, the assumption that the normal individuals married into the family are heterozygous for different modifying genes which may change (enhance or diminish) the effect of the gene for brachyphalangy in question. It was possible to show that the gene *B* and the modifying gene (M_B) were not linked.

Irregular Expression of Genes.

It is obviously not possible to do much more than mention some of the phenomena observed in the genetics both of man and of experimental animals which at first glance seem to obey no Mendelian law. Let me illustrate with some examples of what appears to be an irregular expression of genes.

Occasionally in examining the pedigree of a family showing the effect of a dominant gene, we may find what at first sight appears to be a skipping of a generation, that is an individual, offspring of an affected parent, having affected offspring but himself (herself) apparently not affected. This is really an example of the irregular expression of the gene controlling the character concerned, and generally the genetic picture can be established by study of the progeny, as mentioned above (and see below, in the discussion of Huntington's chorea).

In cases of identical twins (as judged by the accepted criteria) a marked physical defect may be present in one twin only, for example, hare-lip in one and the other quite normal (Stern, 1950).

Another example is that of a definite variation in the manifestation of a rare trait in the same pedigree, as, for example, that of "lobster claw" or "cleft hand", an abnormality due to a single gene which is inherited as a dominant. A classical case is that illustrated in Figure VI in which we have an affected mother who by three different husbands had five children similarly affected, but all differing in the degree of malformation. It is obvious that the same dominant gene is operating in all cases, derived from the mother, but acting in a slightly different environment in each case and so having variable expression in the phenotypes (Stern, 1950). Five families with this gene are known in England (Haldane, 1948).

Again, the type of condition I have just illustrated is exemplified in "blue sclerotics"—an eye condition harmless in itself, but at times associated with serious defects of other parts of the body, including otosclerosis and more or less excessive fragility of bones. The medical literature contains many descriptions of this inherited condition.

[1] This series is dealt with briefly not because it is unimportant, but rather because the genetics of blood-group inheritance is a large field in itself and would be familiar to you all, even if only in a general way. But it is proper to mention that so important has the study of genetics of the non-adaptive characters of man become that an an attempt is now being made to base anthropology on genetics instead of on the older systems of bone measurement and skull conformation (Boyd, 1950). And of the few genetically defined non-adaptive characters so far available for study the blood-groups are by far the most important.

[2] In connexion with congenital abnormalities we may note that it has been suggested that rhesus incompatibility may be of importance in many cases of undifferentiated mental deficiency—milder forms of kernicterus and associated functional disturbances from the same cause (Gruenwald, 1947).

A remarkable example of variation in the expressivity of a gene is found in the variable age of onset of such a genetically caused disease as Huntington's chorea. It is stated that the usual age of onset of this very serious incurable nervous disease is in early middle age. But this generalization conceals a very important truth about the great variation in the age of onset. I have prepared a graphic representation based on Bell's 460 cases to show the age of onset (Figure VII, based on table in Stern, 1950). As you can see, the most frequent age of onset of the condition does lie between thirty and forty years, but, as the graph shows, the disease may occur during the first years of life, or as late as sixty or more years.

Now, "pedigree study shows that the trait is clearly hereditary, occurring only in certain families and usually transmitted from one affected parent to half of the children". But "this simple picture of dominance is disturbed by the variable age of onset". Genetic analysis shows that only the same main gene seems to be concerned

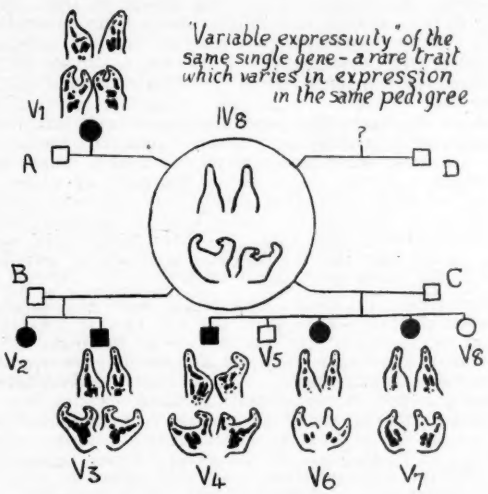

FIGURE VI.

Pedigree of "lobster claw" in three separate families of one affected mother (IV8) by three separate fathers, A, B and C. (From Stern, 1950.)

in all pedigrees, so that the differences among individuals appear to be due to modifying genes and the like, that is, to differences in the internal environment of affected individuals.

This variation in the age at which a gene's effect is unmasked helps to explain the apparent "skipping of generations" (not only, of course, in Huntington's chorea). As you know, often enough choreic children are born to normal-appearing parents, although one of them is heterozygous for the allele *Ht* which causes the disease. If the genotypically affected parent dies before having shown choreic symptoms and half the children develop the disease, an exception from the rule of typical dominance may be recorded. Obviously this is quite possible, as in over 21% of cases the age of onset is forty-five years or more; and the less the age of the parent at death, the more likely there is to be an apparent skipping of a generation owing to incomplete penetrance; and equally obviously, the greater the age of the parents at death, the less pronounced this incomplete penetrance becomes.

This phenomenon of variation in age of onset of hereditary disease occurs in other conditions thought to be determined by a single gene.

Now, in all the examples which I have mentioned we can see variations in the expression of the gene in the phenotype, that is the actual individual. The quality of the gene concerned in this variability is called its "degree of penetrance". As the gene has to act in such complex and possibly varied environment, we can well imagine "the production of variable phenotype, in spite of invariable genes". Differences in genic expression, then, are variable consequences of the same "main" gene. It would appear that the variability in the expression of the gene is probably due to variation in the course of reactions in the developing zygote (Weiss, 1950). While it was shown some years ago by Ford and Huxley that genes control rates of processes in the body and the time of their onset, it is obvious that the genes themselves cannot act independently of the internal environment, including "modifying genes", and that in this fact lies the explanation of variabilities of penetrance and expressivity.

Lethal Genes and Pre-Natal Death.

You will all be familiar with the fact that spontaneous abortion in the early months of human pregnancy is a far from uncommon occurrence. Now, while it seems to be practically certain that in some of these cases the fault

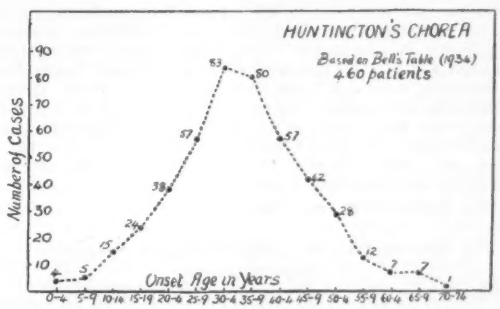

FIGURE VII.

Huntington's chorea. Graph to show distribution of 460 cases in terms of age of onset of disease. (Based on Bell's table, 1934, in Stern, 1950, page 270.)

lies in the maternal uterine mucosa and may be remediable ("a good egg in a bad environment"), it seems very probable that in many cases the abortion takes place because of the death of a faulty fœtus which fails to become embedded or is embedded imperfectly owing to its own internal defects ("a bad egg in a good environment").

We have seen above that probably something more than 30% of mammalian embryos are abnormal and that of these a fair proportion are already defective in the phase of segmentation, before implantation has begun. "Thus, ability of an ovum to implant even though it is or subsequently becomes defective, probably requires more robustness of the embryo than does mere segmentation." Where the ovum is very abnormal and fails to become embedded, probably no period would have been missed at all; the pregnancy would not even have been known to exist. It is the loss of the implanted ovum that constitutes what is usually known as abortion.

What might be called the clinical evidence of the high rate of pre-natal death in mammalian forms has already been given in an earlier section, on "pre-natal death". Here I should like to mention the compelling evidence (based on breeding and pathological studies) for the homozygosity of a lethal gene as a cause of pre-natal death in an experimental animal.

The typical lethal gene is always regarded as harmless in the heterozygous condition and so is transmitted and perpetuated by organisms which do not appear to suffer from its presence. But when an offspring of two heterozygous parents carries a lethal gene (of the same locus) from each parent, then we have the homozygous condition and the lethal genes produce their full fatal effects.

The "yellow" mouse is "the classical case of a mammalian lethal gene", and one in the analysis of whose genetics we can find an explanation of many obscure phenomena, including pre-natal death and "spontaneous" abortion (Grüneberg, 1943; also Needham, 1942). The

"yellow" gene (*Av*) is fully dominant. It was early observed that all yellows were heterozygotes and that no homozygous (pure breeding) yellow mice (*Av/Av*) were obtainable. Careful genetical and histological studies by several workers showed that homozygous yellow embryos (*Av/Av*) were produced in the expected Mendelian proportion, but that in the homozygous condition the gene for yellow invariably led to the early death of the embryos (before the eighth day of gestation), in most cases before implantation had occurred. But there is more to lethal yellow than this. For example, the heterozygous condition in the female involves an endocrine disorder which possibly produces defective intrauterine conditions leading to early pre-natal death of a proportion of embryos from matings with normal (non-yellow) mice.

It is conceivable that a certain proportion of "normal" pre-natal death (Robinson, 1921) may be due to the homozygous occurrence of genes which, fairly commonly occurring in the heterozygous condition, have no effect on gross structure and no apparent physiological or biochemical effects, but which occurring in the homozygous condition, especially if in the presence of modifying genes with a marked depressing effect on viability, cause the early death of the zygote.[1] Or, possibly, the heterozygous condition for certain genes in the mother may have effects on intrauterine conditions, comparable to those thought to occur in the female yellow mouse, leading to the death of the ovum at a very early stage of development. More probably some of the abnormal zygotes are due to the action of newly occurring lethal genes, which have arisen by "spontaneous" mutation.

Such, however, is only speculation.

Genetic Factors in Mammalian Congenital Abnormalities.

One of the great difficulties in elucidating the genetic factors in the production of human congenital abnormalities lies in the impossibility of setting up statistically valid experiments. In the case of human abnormalities we are confined to general population analysis and pedigree analysis. But a great amount of analogical support is derived from well controlled mammalian studies, as has already been seen.

In both rats and mice, which are easy to rear, numerous in progeny, and with a great turnover of generations within a few years, there are now well-established true-breeding strains which show genetically determined defects. For the mouse the material available has been admirably collected by Hans Grüneberg in his "The Genetics of the Mouse" (1943).

I propose to illustrate two major points from this mammalian material: (*a*) the continuous gradation of abnormality; (*b*) the possibility of multiple abnormalities due to the action of a single gene. In some cases the same strain of animals illustrates both points; and some of the material already discussed has also provided similar illustrations.

Continuous Gradation of Abnormality.

Otocephaly in guinea-pigs is a condition which illustrates the wide range of variation possible in the phenotypes of an established hereditary abnormality. Leaving aside the details of genetic analysis, the most striking feature in this abnormality is the remarkable range in the degree of disorganization found. A whole series of examples shows how in the least abnormal group the true mouth is mildly restricted in size; then through many intergrades it is increasingly restricted, the ears approach each other ventrally until a median "throat" opening is formed. Next, with the restriction of the mouth-nose area the mouth is altogether lost and the nostrils fuse: in this grade of defect the eyes are moving towards each other ventrally; and in more advanced grades the eyes show varying degrees of fusing to produce cyclopia. In more disorganized grades the eyes completely disappear (anophthalmia); and eventually, in the most disorganized grades, there is no sign of a head at all (Wright and Wagner, 1934).

This continuous gradation of abnormality is found in many other animals, including man.

Multiple Effects of a Single Gene.

Genes are usually named for whatever is the most prominent (or the first discovered) effect produced by them. For example, in speaking of a mutation in *Drosophila* called "vestigial", we mean the gene which produces vestigial wings. The convenience of such a system of nomenclature should not give us the idea that named genes affect only the characteristics implied by their names. On the contrary there is reason to believe that practically every gene which the organism possesses exerts some effect on almost all the other characteristics. Thus the gene "vestigial" in *Drosophila* not only reduces wing-size, but modifies the balancers, causes certain bristles to be erect instead of horizontal, changes the wing muscles, changes the shape of the spermatheca and alters the rate of growth, the fecundity, and the length of life. From evidence such as this, including evidence from mammalian forms, "we may conclude that the function of the gene is far more vital than merely producing a change in the colour of the eye, the shape of the wing, or characteristics of the hair".

Let me illustrate this point from some well established examples of genetically determined mammalian abnormalities. In these cases it would appear that a single gene can produce a wide variety of effects, some of which are caused by other preceding effects, but the sum total of which it is difficult to relate to any common factor. Needham (1942) says that "In these 'pleiotropic' cases, it is likely that the fundamental anomaly is metabolic, manifesting itself in different ways".

Emphysemic in Rats. One lethal gene discovered by Grüneberg (1938) occurs in the rat and is tentatively named "emphysemic" for convenience by Needham (1942). In this the primary fault is an anomaly of cartilage formation, which, quite distinct from achondroplasia, affects particularly the thoracic skeleton, causing the ribs to thicken, the lumen of the trachea to be narrowed, and the thorax to be fixed in a compressed position with a consequent emphysema of the lungs. From this central effect of the primary cause, death may follow in a variety of ways (Needham, 1942).[1]

Grey-Lethal in Mice. Another example is the grey-lethal gene in the mouse, an autosomal recessive, which suppresses the formation of all yellow pigment in the coat, produces serious skeletal abnormalities, and kills the homozygotes at the age of 22 to 30 days. (Needham, 1942.)

Stub (St) in Rats. This is a simple Mendelian recessive that has very deleterious and widespread effects when in the homozygous condition. It reduces the number of tail vertebræ, frequently produces malformations in the posterior region of the body, markedly affects the viability of the young and greatly retards body growth in individuals that survive. The great majority of homozygotes die at birth or soon after—very much as is found in other strains, for example the grey-lethal and yellow-lethal and Danforth's short-tail strains of mice (compare also "creeper" in the fowl). In the non-viable rats there occur such features as defective development or absence of vertebræ, very frequently accompanied by aplasia or atresia of the anus and rectum, penis, vagina and bladder, and developmental defects of the kidneys and ureter; these, in some cases, in association with defects of the pelvis and of the rear legs (including almost complete fusion of the femora) (Ratcliffe and King, 1941). In some cases the assemblage of developmental defects is strikingly reminiscent of that found in many cases of symmelia.

Danforth's Short-Tail (Sd) in Mice (Grüneberg, 1943) is a dominant, with a high lethal effect in the

[1] It may be noted that in pooled pedigrees of (human) hæmophilia there is a significant deficiency of females, due probably to the fact that the homozygous female commonly dies *in utero* (compare Crew, 1947, page 48).

[1] Similarly the short ear gene in the mouse (*se*) has been shown to have widespread though minor effects on cartilage and bone, possibly producing its effects through a primary interference with cartilage formation. The gene seems to be associated also with anomalies of kidneys and diaphragm (Green, 1951).

heterozygous condition and completely lethal in the homozygous. Its effects are manifested in varying degrees of defect of the caudal, sacral and lumbar vertebræ and in varying degrees of malformation of all the organs of the posterior body region.[1]

These must suffice as illustrations of the multiple effects of a single gene.

The Classical Case—Myelencephalic Blebs in the Mouse.

If you will bear with me a little longer I should like to tell you a most remarkable story of an inherited abnormality in mice, known as the "myelencephalic bleb".[2] And I will deal with this rather fully, for several reasons. In the first place, we have an illustration of how an apparently minor deviation from normal development can produce multiple and widespread effects, which at first sight would appear to have nothing to do with each other. Further, in the great series of abnormals we find a wide distribution of the degree of abnormality (as we see in *sympus dipus*), which may be an example of the effects of modifying factors, genetic and otherwise, and an illustration of variation in "penetrance". Again, in the whole work is to be seen a beautiful example of the application of many techniques—animal genetics, refined experimentation, statistical analysis, and so on. Finally we have a striking illustration of Needham's postulate for advance in embryological knowledge—the dynamic balance between observation, speculation and experiment.

In 1924 Little and Bagg obtained a strain of mice after X-ray irradiation (but only doubtfully due to that irradiation: Grüneberg, 1943) which showed the presence of lethal genes causing the following effects:

1. Anomalies of the eye varying from slight atrophy of the lid to marked atrophy of the eye itself, often enough accompanied by an asymmetry of the skull and in a few cases reduction in size of the ear.

2. Anomalies of the foot and limbs of very varied types, asymmetrical in occurrence, including: syndactylism, with maybe severe clubbing and dorsal flexion; hypodactylism; congenital amputation; polydactylism (digital reduplication).

3. Anomalies of hair growth in the saddle region.

4. Anomalies of the kidney, varied in type: absence of kidney, ureter and renal vessels on one side; varying degree of hydronephrosis; congenital absence of both kidneys.

5. Disorganizations of the head, including severe reductions of the lower jaw and anomalies of the tongue.

It was demonstrated conclusively by breeding experiments that effects 1, 2 and 3 of the above list are caused by a single gene; the relation of 4 to 1, 2 and 3 is not clear; the anomalies 5 are certainly independent of the other effects.

In 1924 Bagg and Little discovered that some of the new-born young, and a larger fraction of late embryos, show extravasations of blood under the skin, mostly on the head in the eye region, but occasionally also on the feet.

In 1929 Bagg, by inventing a technique which enabled him by Cæsarean operation to observe living embryos through the transparent uterine wall without interfering with the progress of pregnancy and to remove some fœtuses from the uterus and mark others by snipping off their tails, had succeeded in showing that the limb anomalies are associated with the presence of blisters (or blebs) and clots at the extremities which interfere with the fore-limb and hind-limb "fields"; and that the hæmorrhagic lesions observed in the 14 to 15 day embryos were preceded by the presence under the skin of blisters filled with a colourless fluid in 12 to 13 day embryos. These blebs are localized in much the same way as the foot and eye anomalies. Hæmorrhage into some, but not all, of the blebs causes a mechanical interference with developing organs, such as feet and eyes, and so produces anomalies. "The kind of anomaly was clearly a consequence of the size and location of a bleb, and it was clear that normal overlap would occur whenever such blebs happened not to interfere with developing structures, or when they became absorbed before damage had been done." Bagg assumed that the hæmorrhages into the blebs were consequences of the pressure exerted by the blebs on underlying blood capillaries.

In 1933 Plagens showed that the blood clots are formed deeper in or under the skin, usually under the pressure of a preexisting bleb. These "thrombi" were supposed to be responsible for most of the morphological abnormalities later observed. But the origin and distribution of these blebs and "thrombi" were still unknown.

The solution was discovered by Bonnevie in 1934 by a study of the embryology of the condition. Working on a large range of homozygous embryos, she was able to show that the blebs were due primarily to a single functional defect in the development of the nervous system, operative from the seventh day of embryonic life. She showed that there is a normal embryonic feature in the higher vertebrates, namely the transitory presence of a *foramen anterius* in the roof of the myelencephalon, anterior to the site where the choroid plexus is to be formed, which foramen acts as a regulator of the pressure of the cerebro-spinal fluid during the foldings of the brain. The foramen disappears again early. Now, in the "lethal mice" (*my/my*) this normal opening in the roof of the hind brain (not to be confused with the foramen of Magendie) allows a large quantity of the cerebro-spinal fluid to escape. The fluid forms blisters under the epidermis, first on the dorsal surface of the head and neck, close to the foramen, and then gradually spreads all over the surface of the body; some is carried into the limb bud districts and so into the limbs to give rise to syndactyly, polydactyly *et cetera* and to interfere in various ways with the normal limb pattern. Others move in front of the eye cups and lens. As time goes on the capillaries on the floor of a blister weaken, discharging their blood into it and forming in many cases hæmatomata. The blebs and hæmatomata interfere mechanically with differentiating organs, in whose neighbourhood they may happen to lie. Now the escape of fluid into the area between the embryonic epidermis and corium is quite normal; but in these *my/my* mice the process of bleb formation is greatly exaggerated. This may be due to an over-production of cerebro-spinal fluid; or it may result from insufficient reabsorption. Which, is not known.

Bonnevie also showed that the distribution of the blebs is conditioned by the surface relief of the embryo, the blebs tending to pass along the planes of least resistance along the curvatures of the body, and the asymmetrical distribution of the limb anomalies probably resulting from the fact that the young mouse embryos are twisted in a right hand spiral which causes a considerable difference in tension in the epidermis of the two sides. Bonnevie has gone further and shown the probable mode of action of the modifying genes which localize the effect of the *my* gene to various regions of the body; and she has shown that genetic factors influencing the surface relief of the embryo secondarily influence the path which the blebs take.[1]

We see then that in this complex genetic and anatomical problem the task was successfully undertaken to discover by embryological analysis a mechanism which would explain: (*a*) the origin of the divers morphological anomalies; (*b*) their peculiar but orderly distribution; (*c*) why and how normal overlaps can occur; and, lastly (*d*) the way in which modifying genes can enhance or even abolish the gene manifestation or direct it towards

[1] Compare also Amputated, a recessive lethal in cattle (Wriedt and Mohr, 1928).

[2] This account is based on Grüneberg (1943), and Needham (1942).

[1] The genetic relations of the kidney anomalies to the gene for myelencephalic blebs are not clear. There is a suggestion that a single gene is responsible for eye and kidney anomalies, but the data are too scanty for a conclusive proof. It would seem, possibly, that either two linked genes, or the same gene, are responsible for both conditions. In the latter case, modifying genes evidently favour this particular type of manifestation.

one part of the body or another. As Grüneberg (1943) has well said:

> How a very complex genetic situation found its complete explanation through the discovery of an entirely new, but comparatively simple, embryological mechanism forms one of the most thrilling episodes in the history of genetics and deserves to be more widely known by pathologists in general and teratologists in particular.

General Remarks.

In all these animal series we are dealing with material which has been subjected to full genetical analysis, so that the question of genetic as against environmental causation would appear to be settled. Whatever be the details of the mechanisms by which the anomalies discussed are brought about, I think that it will be agreed that we can see some remarkable resemblances to the occurrence of abnormalities in the symmelian forms (and indeed in several other forms of human abnormality). One striking thing about all of these cases is the way in which they can be arranged in a continuous progressive series of increasing disorganization of a system—skeletal, urogenital *et cetera*—suggesting that the conditions under examination are influenced by modifying genes (that is, we have examples of variation in "penetrance"). Again, we see that in the majority of cases the effects of a single gene are found in more than one bodily system; and also that the degree of disorganization in one system is not necessarily correlated with that in another.

These and other features would appear to lend support to the hypothesis that the symmelian monstrosity (and many other abnormal forms—especially the grossly abnormal) may be the manifestation of a single "spontaneously" mutated gene or of rare homozygous recessive genes producing effects upon more than one bodily system, and varying in its (their) effects in different cases owing to the different environment in which it is operating. On the other hand, the effects of extreme vitamin deficiency, X irradiation and, to some extent, infectious disease also show some remarkable similarities to the genetically determined effects. So that here we must leave the matter with the verdict of "*non liquet*—not proven".

Conclusion.

If it is thought that too much space has been devoted to modern experimental teratogenesis and to genetic work, I can only plead that the work is so significant for the main problem and generally so little known to the busy practitioner that it seems reasonable to set out in some detail certain parts of the available evidence.

Properly speaking, the scope of this lecture does not necessarily entail an evaluation of the theories discussed; but we might ask: what conclusions have we reached on the various theories of causation of congenital anomalies? It is clear that we can say definitely that some conditions are demonstrably determined by environmental factors, and that certain other conditions are genetically determined. But this preliminary delimitation leaves a large field in which the causative factor (or factors) is still to seek, although in certain specific instances the available evidence may be suggestive of a genetic or of an environmental explanation or of a combination of both. We have a further complication in that certain abnormal conditions appear to be able to be produced either by genetic or by various environmental factors. Indeed, it is probably true that although the mechanisms by which anomalies are produced are rather few, the potentially teratogenic agents are quite numerous, as is suggested by both clinical and experimental evidence: there are possibly many, or at least more than one, causes of the same anomaly, and the causes may be environmental as well as genetic. Some malformations observed and recognized as hereditary defects can also be induced by environmental factors, such as a maternal dietary deficiency; a specific malformation can be the result of a genic mutation in one case and of an environmental modification in another (a "phenocopy"). Therefore, it is difficult to be sure in a single instance of supposed hereditary defect whether we are dealing with a phenotype truly reflecting the abnormal genotype or merely a phenocopy due to the operation of environmental factors on a normal genotype.

One danger to be guarded against is the acceptance of any simple "blanket explanation" of the causation to cover the remarkable variety of cases of congenital abnormality seen. There is an inevitable tendency, when a new theory is developed and reasonably well established for a particular anomaly or syndrome of anomalies either on experimental or clinical grounds, for workers to look to the new theory as an over-all explanation. This may cause us to neglect other well-established evidence from which quite different theoretical inferences can be drawn. This tendency is exemplified in the way Stockard's theory of environmental teratogenesis appeared to sweep many people off their feet; in the later rather general acceptance of a predominantly genetic theory (compare Hamilton, Boyd and Mossman, 1945[1]); and, in the last decade, in the way the stimulus of Gregg's work has tended with some to an over-emphasis on environmental factors with a possible neglect or undervaluation of the genetic factors (as in Ingalls, 1950, and possibly Dods, 1948).

Further, the facile use of such expressions as "defect of the germ plasm", "critical period" and the like reminds us of a further danger—in the loose use of terms and in the assumption that giving a condition or a process a name explains it or gives it reality. As Needham (1934) has pointed out, the invention and clarification of terms is one of the greatest limiting factors in scientific advances. The validity of such terms as "organizer", "evocator", "induction", "critical period" and the like must be carefully established in their meanings. And Weiss (1950) has warned us of the dangers of the tendency "to oversimplify morphogenetic phenomena by the use of terms and concepts based on premature generalisation and not corresponding to the realities of the complete situation".

The fact is that each type of defect must be studied intensively and separately and the conclusions reached should be guardedly tentative. And our findings must be submitted to every test possible, experimental, clinical and statistical; for, as Francis Galton wrote:

> General impressions are never to be trusted. Unfortunately when they are of long standing they become fixed rules of life, and assume a prescriptive right not to be questioned. . . . But it is the triumph of scientific men to rise superior to such superstitions, to desire tests by which the value of beliefs may be ascertained, and to feel sufficiently masters of themselves to discard contemptuously whatever may be found untrue.

Acknowledgements.

I take this opportunity of thanking Dr. J. F. Dunkley and Dr. W. Simmons for making the original specimen of *sympus* available to me, Professor Sir Peter MacCallum (Melbourne), Dr. H. Bettinger (Melbourne Women's Hospital) and Professor B. T. Mayes (Sydney) for allowing me the use of valuable fœtal material, Professor S. Sunderland (Melbourne) and the members of his department for their ready and generous hospitality to me, Professor H. J. Wilkinson and Professor A. J. Canny (Brisbane) for discussing some aspects of the problem, the Commonwealth X-ray and Radium Laboratory (Melbourne, Director, Dr. C. E. Eddy) for help with radiographs, Mr. Knight (X-ray Department, Brisbane General Hospital), Mr. E. Bagnall and Mr. G. Thompson (Medical School, Brisbane) for technical assistance, and the National Health and Medical Research Council for a grant to meet part of the travelling expenses involved in the work on symmelian abnormalities.

Bibliography.

Albaugh, C. H. (1945), "Congenital Anomalies Following Rubella in Early Pregnancy", *J.A.M.A.*, 129: 719.

Aristotle (1943), "On the Generation of Animals", Heinemann, London.

Aycock, W. L. and Ingalls, T. H. (1946), "Maternal Diseases as a Principle in the Epidemiology of Congenital Anomalies", *Am. J. M. Sc.* 212: 366.

[1] "Most abnormalities of development, then, can be attributed to genetic causes. These may be in the nature of mutations, but they frequently result from the action of genes (dominant or homozygous recessive) which operate adversely on some process of development."

BALLANTYNE, J. W. (1902, 1904): "Manual of Antenatal Pathology and Hygiene", I. The Fœtus, II. The Embryo, Green, Edinburgh.

BIRCH-JENSEN, A. (1949), "Congenital Deformities of the Upper Extremities", *Domus Biol. Hered. Human. Universitatis Hafniensis*, Denmark.

BOYD, W. C. (1950), "Genetics and the Races of Man", Little, Brown, Boston.

CARNEGIE YEAR BOOK, Number 46 (1946-1947), Report of Department of Embryology, Director G. W. Corner, 107.

CORNER, G. W. (1920), "A Note on Very Early Pig Embryos Showing Degenerative Changes", *Anat. Rec.*, 18 : 229.

CREW, F. A. E. (1947), "Genetics in Relation to Clinical Medicine", Oliver and Boyd, Edinburgh.

DODS, L. (1949), "Progress in Pædiatrics", M. J. AUSTRALIA, 2 : 781.

FARABEE, W. C. (1905), "Inheritance of Digital Malformations in Man", Papers of Peabody Museum, Harvard University, 3 : 65.

FOGH-ANDERSEN, P. (1942), "Inheritance of Harelip and Cleft Palate *et cetera*", *Nyt Nardisk Forlag*. Arnold Busck, Copenhagen.

FORD, E. B. (1942), "Genetics for Medical Students", Methuen, London.

GARROD, A. E. (1902), "The Incidence of Alkaptonuria : A Study in Chemical Individuality", *Lancet*, 2 : 1616.

GILLMAN, J., GILBERT, C., GILLMAN, T., and SPENCE, J. (1948), "A Preliminary Report on Hydrocephalus, Spina Bifida and Other Congenital Anomalies in the Rat Produced by Trypan Blue", *South African J. M. Sc.*, 13 : 47.

GREEN, M. C. (1951), "Further Morphological Effects of the Short Ear Gene in the House Mouse", *J. Morphol.*, 88 : 1.

GREGG, N. McA. (1941), "Congenital Cataract Following German Measles in the Mother", *Tr. Ophth. Soc. Australia* (B.M.A.), 3 : 35.

GRÜNEBERG, H. (1943), "The Genetics of the Mouse", Cambridge University Press, 31, 201, 103.

GRUENWALD, P. (1947), "Mental Deficiency of Prenatal Origin : A Challenge to Preventive Medicine", *Am. J. M. Sc.*, 214 : 605.

HALDANE, J. B. S. (1948), "The Formal Genetics of Man", Croonian Lecture, *Proc. Roy. Soc. Lond.*, S.B., 135 : 147.

HALE, F. (1933), *J. Hered.*, 24 : 105 ; cited by Warkany and Schraffenberger (*loc. cit.*, 1944).

HALE, F. (1935), "The Relation of Vitman A to Anophthalmos in Pigs", *Am. J. Ophth.*, 18 : 1087.

HAMBURGER, V., and HABEL, K. (1947), "Teratogenic and Lethal Effects of Influenza-A and Mumps Viruses on Early Chick Embryos", *Proc. Soc. Exper. Biol. & Med.*, 66 : 608.

HAMILTON, W. J., BOYD, J. D., and MOSSMAN, H. W. (1945), "Human Embryology", Heffer, Cambridge.

HARVEY, WM. (1847), "Anatomical Exercises on the Generation of Animals", in Latin (1651), trans. R. Willis, "The Works of William Harvey, M.D.", The Sydenham Society, London.

HERTIG, A. T. (1951), Figures in Cunningham's "Text-book of Anatomy", Ninth Edit., 16.

HERTIG, A. T., and ROCK, J. (1944), "On the Development of the Early Human Ovum, with Special Reference to the Trophoblast of the Pre-villous Stage : A Description of 7 Normal and 5 Pathologic Human Ova", *Am. J. Obst. & Gynec.*, 47 : 149.

HERTIG, A. T., and ROCK, J. (1945), "Two Human Ova of the Pre-villous Stage, Having a Developmental Age of About Seven and Nine Days Respectively", Contrib. Embryol. (No. 200), 31 : 65, Carnegie Instit., Washington.

HEUSER, C. H., ROCK, J., and HERTIG, A. T. (1945), "Two Human Embryos Showing Early Stages of the Definitive Yolk-Sac", Contrib. Embryol. (No. 201), 31 : 85, Carnegie Instit., Washington.

HOGBEN, L. (1950), "The Methodology of Medical Genetics", in "Research in Medical Science", 63, Macmillan, New York.

INGALLS, T. H. (1947), "Etiology of Mongolism : Epidemiologic and Teratologic Implications", *Am. J. Dis. Child.*, 74 : 147.

INGALLS, T. H. (1950), "Congenital Malformations", in "Research in Medical Science", 422, Macmillan, New York.

JACKSON, E. S. (1931), "Some Voyages Connected with the Discovery of Australia : Their Medical History", M. J. AUSTRALIA, 2 : 735.

JOB, T. T., LEIBOLD, G. J., and FITZMAURICE, H. A. (1935), "Biological Effects of Roentgen Rays : The Determination of Critical Periods in Mammalian Development with X-Rays", *Am. J. Anat.*, 56 : 97.

JOHNS, F. S. (1946), "Congenital Defect of the Abdominal Wall in the New Born (Gastroschisis)", *Ann. Surg.*, 123 : 886.

LANDTMAN, B. (1948), "On the Relationship Between Maternal Conditions During Pregnancy and Congenital Malformations", *Arch. Dis. Childhood*, 23 : 237.

LEVINE, P., BURNHAM, E., KATZIN, E. M., and VOGEL, P. (1941), "Role of Iso-immunization in Pathogenesis of Erythroblastosis Fetalis", *Am. J. Obst. & Gynec.*, 42 : 925.

MALL, F. P. (1908), "A Study of the Causes Underlying the Origin of Human Monsters (Third Contribution to the Study of the Pathology of Human Embryos)", *J. Morphol.*, 19 : 3.

MOHR, O. L., and WRIEDT, C. (1919), "A New Type of Hereditary Brachyphalangy in Man", Carnegie Institute of Washington, Publication No. 295.

MULLER, H. J. (1950), "Radiation Damage to Genetic Material", *Am. Scientist*, 38 : 399.

MURPHY, D. P. (1929), "The Outcome of 625 Pregnancies in Women Subject to Pelvic Radium or Roentgen Irradiation", *Am. J. Obst. & Gynec.*, 18 : 179.

MURPHY, D. P. (1947), "Congenital Malformations : A Study of Parental Characteristics with Special Reference to the Reproductive Process", Second Edit., Lippincott, Philadelphia.

MURPHY, D. P., and GOLDSTEIN, L. (1929), "Etiology of the Ill-Health of Children Born After Maternal Pelvic Irradiation", *Am. J. Roentgenol.*, 22 : 207, 322.

NEEDHAM, J. (1934), "A History of Embryology", Cambridge University Press.

NEEDHAM, J. (1942), "Biochemistry and Morphogenesis", Cambridge University Press.

NEEL, J. V. (1951), "Some Applications of the Principles of Genetics to the Practice of Medicine", *Med. Clin. North America*, March, 519.

PATRICK, R. (1948), "Report of a Survey of Children Born in 1941 with Reference to Congenital Abnormalities Arising from Maternal Rubella", M. J. AUSTRALIA, 1 : 421.

PATTEN, BRADLEY M. (1947), "Human Embryology", Blakiston, Philadelphia.

PENROSE, L. S. (1950), "Value of Genetics in Medicine", *Brit. M. J.*, 2 : 903.

PLINY (1947), "Natural History", Heinemann, London.

RATCLIFFE, H. L., and KING, H. O. (1941), "Developmental Abnormalities and Spontaneous Diseases Found in Rats of the Mutant Strain, Stub", *Anat. Rec.*, 81 : 283.

ROBERTS, J. A. F. (1940), "An Introduction to Medical Genetics", Oxford University Press.

ROBINSON, ARTHUR (1921), "Prenatal Death", Struthers Lecture of 1920, *Edinburgh M. J.*, March, 137, 209.

ROCK, J., and HERTIG, A. T. (1942), "Some Aspects of Early Human Development", *Am. J. Obst. & Gynec.*, 44 : 973.

ROCK, J., and HERTIG, A. T. (1948), "The Human Conceptus During the First Two Weeks of Gestation", *Am. J. Obst. & Gynec.*, 55 : 6.

SAINT-HILAIRE, I. G. (1836), "*Histoire (générale et particulière) des anomalies de l'organisation chez l'homme et les animaux*)", Paris.

SOUTHWICK, W. E. (1939), "Time and Stage in Development at which Factors Operate to Produce Mongolism", *Am. J. Dis. Child.*, 57 : 68.

STERN, CURT (1950), "Principles of Human Genetics", Freeman, San Francisco, 292, 270.

STOCKARD, C. R. (1920-1921), "Developmental Rate and Structural Expression : An Experimental Study of Twins, 'Double Monsters' and Single Deformities, and the Interaction Among Embryonic Organs during their Origin and Development", *Am. J. Anat.*, 28 : 115.

STREETER, G. L. (1930), "Focal Deficiencies in Fetal Tissues and Their Relation to Intrauterine Amputation", Contrib. Embryol. (No. 126), 32 : 1, Carnegie Instit., Washington.

SWAN, C., TOSTEVIN, A. L., MOORE, B., MAYO, H., and BARHAM, BLACK, G. H. (1943), "Congenital Defects in Infants Following Infectious Diseases During Pregnancy, with Special Reference to the Relationship between German Measles *et cetera*", M. J. AUSTRALIA, 2 : 201.

SWAN, C. (1948), "Rubella in Pregnancy as an Ætiological Factor in Stillbirth", *Lancet*, 2 : 744.

SWAN, C. (1949), "Rubella in Pregnancy as an Ætiological Factor in Congenital Malformations, Stillbirth, Miscarriage and Abortion", *J. Obst. & Gynec. Brit. Emp.*, 56 : 341, 591.

WARKANY, J. C., and NELSON, R. C. (1940), "Appearance of Skeletal Abnormalities in Offspring of Rats Reared on Deficient Diet", *Science*, 92 : 383.

WARKANY, J. C., and NELSON, R. C. (1941), "Skeletal Abnormalities in the Offspring of Rats Reared on Deficient Diets", *Anat. Rec.*, 79 : 83.

WARKANY, J. C., and ROTH, C. B. (1948), "Congenital Malformations Induced in Rats by Maternal Vitamin A Deficiency", II. Effect of Varying the Preparatory Diet upon the Yield of Abnormal Young, *J. Nutrition*, 35 : 1.

WARKANY, J. C., and SCHRAFFENBERGER, E. (1944), "Congenital Malformations of the Eyes Induced in Rats by Maternal Vitamin A Deficiency", *Proc. Soc. Exper. Biol. & Med.*, 57 : 49.

WARKANY, J. C., and SCHRAFFENBERGER, E. (1946), "Congenital Malformations Induced in Rats by Maternal Vitamin A Deficiency. Defects of the Eye", *Arch. Ophthal.*, 35 : 150.

WARKANY, J. C., and SCHRAFFENBERGER (1947), "Congenital Malformations Induced in Rats by Roentgen Rays. Skeletal Changes in the Offspring Following a Single Irradiation of the Mother", *Am. J. Roentgenology*, 57 : 455.

WEISS, P. (1950), "Perspectives in the Field of Morphogenesis", *Quart. Rev. Biol.* 25 : 177.

WILSON, J. G., and KARR, J. W. (1951), "Effects of Irradiation on Embryonic Development", *Am. J. Anat.*, 88 : 1.

WILSON, J. G., and WARKANY, J. C. (1948), "Malformations in the Genitourinary Tract Induced by Maternal Vitamin A Deficiencies in the Rat", *Am. J. Anat.*, 83 : 357.

WILSON, J. G., and WARKANY, J. C. (1949), "Aortic-arch and Cardiac Anomalies in Offspring of Vitamin A Deficient Rats", *Am. J. Anat.*, 85 : 113.

WRIEDT, C., and MOHR, O. C. (1928), "Amputated, a Recessive Lethal in Cattle, with a Discussion of the Bearing of Lethal Factors on the Principles of Livestock Breeding", *J. Genet.*, 19 : 187.

WRIGHT, S., and WAGNER, K. (1934), "Types of Subnormal Development of the Head from Inbred Strains of Guinea Pigs and their Bearing on the Classification and Interpretation of Vertebrate Monsters", *Am. J. Anat.*, 54 : 383.

Reports of Cases.

COARCTATION OF AORTA WITH MULTIPLE CONGENITAL ABNORMALITIES.

By HARRY M. WINDSOR,
Sydney.

R.S., a jockey, aged eighteen years, was referred by Dr. John Guyot because of hypertension. He was found to be suffering from a severe degree of coarctation of the aorta, with moderate cardiac enlargement. His blood pressure was 240 millimetres of mercury, systolic, and 130 millimetres, diastolic. He had no symptoms and thoroughly enjoyed the vigorous open-air life of a country jockey.

In the course of examination the following abnormalities were noted: (i) Torticollis. The boy's mother stated that after an operation for congenital squint this disability had become minimal. (ii) A laparotomy scar. The laparotomy had been carried out because of intestinal obstruction due to a twisted Meckel's diverticulum. (iii) Diffuse generalized congenital ichthyosis. (iv) The well known signs of coarctation of the aorta.

An X-ray examination of the chest revealed notching of the ribs, cardiac enlargement and large bilateral cervical ribs.

In view of the high blood pressure and the cardiac enlargement, operation was advised. This was carried out on October 23, 1952. At operation the following three more congenital abnormalities were noted: (i) a left superior *vena cava*, (ii) a left *vena azygos*, the arch of which lay astride the coarctated part of the aorta, and (iii) a patent *ductus arteriosus*. The coarctation lay three-quarters of an inch distal to the subclavian artery. There was considerable post-stenotic dilatation of the distal aortic segment. Resection of the coarctated section and division of the ductus were carried out. The continuity of the aorta was reestablished by end-to-end anastomosis. The anastomosis was rendered somewhat troublesome by the entrance of the patent ductus into the proximal aortic segment just above the coarctated section.

The boy made a good recovery. He was discharged from hospital on November 15; at that time his blood pressure was 165 millimetres of mercury, systolic, and 85 millimetres, diastolic.

ADVANCED CHRONIC ENDOCARDITIS WITH MITRAL STENOSIS AND AORTIC STENOSIS IN A CHILD OF THREE YEARS.

By BRYAN SHARKEY and VINCENT J. McGOVERN,
Fairfax Institute of Pathology, Royal Prince Alfred Hospital, Sydney.

THE rarity of chronic endocarditis of advanced degree before the age of puberty would indicate that the following case is worthy of record.

On September 29, 1951, D.R., a female, aged three years, was admitted to the Royal Prince Alfred Hospital, Sydney, and the following information was obtained.

Clinical History.

The patient was born three weeks prematurely owing to the occurrence of kidney trouble in the mother during pregnancy. This was the only maternal illness during the pregnancy; there was no history of rubella. The child was apparently normal after delivery and no mention was made of the detection of any abnormality in the post-natal period. Weight at birth was approximately eight pounds; however, the child had never maintained normal growth.

Twelve months prior to admission to hospital it was noticed that she was experiencing attacks of breathlessness, which would occur at any time, but particularly at night. These had become more marked over the last four weeks.

Two weeks prior to admission the child was treated by a local practitioner for pneumonia. Recovery apparently occurred from this episode, but the attacks of breathlessness persisted and were accompanied by circumoral tinges of cyanosis. As before, these occurred especially at night and greatly disturbed the child's sleep. It was also noticed that during such periods of dyspnœa and cyanosis the child's heart beat was audible at a distance.

A cough had been in evidence for at least four weeks. Appetite had always been good, no particular food upsetting her. Bowel motions were always normal. No urinary disturbances had been noted, except for a tendency of late to pass urine without warning—the relatives were unsure as to whether or not the child knew when this was about to occur.

There had never been any vomiting or any indication of pain in the chest or abdomen. Jaundice was never in evidence. Eyesight had apparently always been normal.

FIGURE I.
The stenosed aortic valve.

On the morning of the day of admission to hospital (September 29, 1951) it was noticed that the child's feet and legs were swollen. A local practitioner was consulted and, after administering penicillin and "Neptal", advised the relatives to take the child to hospital.

There had been no previous episodes of œdema, nor had there been feverishness, though the patient was observed to be sweating whilst on the way to hospital.

The mother and father were alive and well. The patient had three sisters (aged seven, six and five years) and one brother. The eldest sister was said to have had breathless attacks at the age of five years, but these had not been experienced since.

The patient was seen to be a somewhat breathless and slightly irritable child. Her weight was 23 pounds 11 ounces. There was no evidence of cyanosis of lips, ears or fingers.

Cardio-Vascular System: The radial arteries were impalpable. The pulse was rapid, but regular in time and amplitude. The pulse wave was well maintained with moderately rapid rise and fall. The pulses were synchronous at both wrists. The femoral pulses were readily palpable and synchronous with those at the wrists.

The thorax showed visible pulsation in its lower half anteriorly owing to a forceful heart beat.

The apex beat appeared diffuse and was palpable maximally in the sixth left intercostal space, three inches from the mid-line (in the anterior axillary line). A diastolic

thrill was palpable in the mitral area climaxing in a palpable systolic shock, and there was a suggestion of a diastolic thrill over the third and fourth left intercostal spaces in the parasternal region. There was a definite aortic pulsation visible and palpable in the epigastrium; the aorta was also palpable in the lower part of the abdomen. No cardiac enlargement was detectable to the right of the sternum.

In the mitral area there was a blowing systolic murmur associated with a presystolic murmur of similar quality culminating in a loud first heart sound. These murmurs were also clearly evident in the third, fourth and fifth left intercostal spaces in the parasternal region. The systolic murmur was audible in the aortic and pulmonary and tricuspid areas.

There was no clubbing of the fingers. Slight venous engorgement was to be seen in the neck. No œdema of legs or ankles was demonstrable at the time of examination.

Respiratory System: The thorax heaved with respiration, the rate being 45 per minute, but the accessory muscles

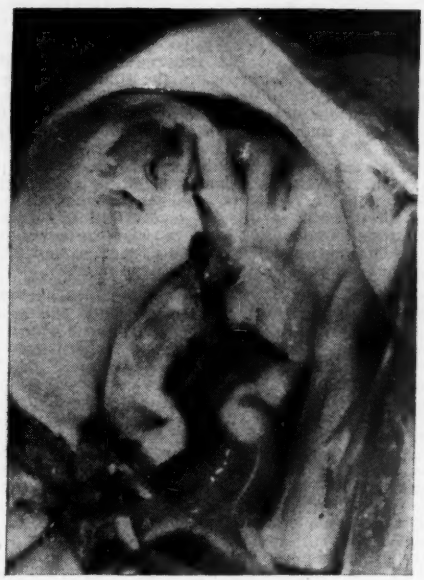

FIGURE II.

The stenosed mitral valve. This has been incised in two places for the purposes of histological examination.

of respiration remained quiescent. The trachea was midline in position. Slight dulness to percussion was detected at the base of the right lung, whilst auscultation revealed discontinuous fine râles at both lung bases.

Abdomen: Aortic pulsations were detected, as stated above. There was a suggestion of tenderness in the right hypochondrium and of a palpable liver. Slight guarding was noted in the right hypochondrium, but there was no rigidity. No masses were palpable in the abdomen.

Hæmatopoietic System: The spleen was not clinically enlarged. There were no palpable lymph glands and no hæmorrhagic phenomena were in evidence.

Treatment in Brief: Treatment comprised the administration orally of tincture of digitalis—28 minims were given on admission, 14 minims were given at eight-hourly intervals for two further doses, after which a maintenance dose of two minims thrice daily was ordered. Oxygen was administered and chloral and bromide sedatives were given.

Hæmatological investigations gave the following data:

Erythrocytes, per cubic millimetre ..	2,460,000
Hæmoglobin, grammes *per centum*	7·8
White cell count, per cubic millimetre ..	24,500
Neutrophile cells	47%
Lymphocytes	44%
Monocytes	7%
Eosinophile cells	2%

The erythrocyte sedimentation rate was 15 millimetres in one hour.

Electrocardiographic examination on October 2, 1951, suggested a vertical heart. Very high peaked *P* waves were apparent in L2. Changes in *ST-T* segment in L1, V5, V6 were suggestive of left ventricular strain, but V1 suggested some right ventricular enlargement.

There was no clinical improvement and the child became more dyspnœic and died on October 3, 1951, four days after admission to hospital.

Autopsy (Summary).

The body was that of a small underdeveloped female child. There was no clubbing of the fingers and no post-mortem venous engorgement was to be seen. The subcutaneous tissues were slightly œdematous.

There were about 100 millilitres of straw-coloured fluid in each pleural cavity and about the same amount of ascitic fluid. There was marked congestion of organs, particularly of the liver.

The heart weighed 155 grammes. The right atrium was not enlarged. The tricuspid ring appeared to be larger than average and there was fairly marked hypertrophy of the right ventricle, the wall at the base being 1·2 centimetres in thickness. The pulmonary valve and artery appeared normal. The left atrium was enlarged and the endocardial surface had a dead white colour. Very marked stenosis of the mitral valve was present. The leaflets had been almost entirely destroyed by fibrosis and the margins where the leaflets should have been were very much thickened. The left ventricle was greatly hypertrophied. Fibrosis of the muscle extended down from the attachment of the chordæ and the ventricular wall measured 2·0 centimetres in thickness. The aortic valve was stenosed and the fibrotic stenosis was such that only a remnant of the anterior leaflet could be seen.

Microscopic Report.—No recognizable Aschoff bodies could be found in the myocardium. Sections from the base of the heart showed some interstitial fibrosis and a section taken from the mitral valve showed that the thickening of the valve was of inflammatory origin. All stages from unorganized fibrin, through granulation tissue to dense scar tissue, were present. Foci of polymorphonuclear leucocytes were also present.

Summary.

This case is presented as one of congestive cardiac failure occurring in a child of three years as a result of advanced, acquired chronic endocarditis with mitral stenosis and aortic stenosis.

A TRAUMATIC GAP IN THE URETHRA.

By V. H. WALLACE,
Melbourne.

INGENUITY and resourcefulness sometimes enable our patients to overcome disabilities without our assistance.

Mr. C., aged forty years, a former stonemason, recently consulted me about the condition of his penis. When he was sixteen years old he was splitting a block of granite. When the stone was partly split he leaned over it. It closed suddenly and nipped the lower surface of the penis, taking a piece completely out, including a portion of the urethra. The wound bled very little and there was not much pain.

An amazing feature of this case is that the patient told nobody about the accident. When he got home from work he trimmed the wound with scissors and a razor blade. His parents and his brothers never knew about it.

At the age of twenty-one years he married, and his wife knew nothing about the injury. He made this comment: "I spent six years in the army without any of the other chaps discovering it." When he wishes to micturate he bends the penis at an acute angle so that there is no obtruction to the flow of urine. He is apt to be considerably embarrassed unless he is entirely alone when passing urine.

A demand was made upon his ingenuity when his wife said that she was anxious to have children. He was equal to the occasion. He obtained a piece of rubber tubing and pushed it along the urethra so that the gap between

FIGURE I.

the severed ends was bridged. The tube passed about two inches towards the *glans penis* and two inches backwards towards the bladder. His spermatozoa reached the tip of the penis and he and his wife now have three children, aged sixteen years, eleven years and four years. Sexual intercourse is normal. The mobile skin of the penis can be made to cover the wound, even when the tubing is in place. The black thread shown in the photograph is to prevent the tube from moving out of position.

An accident such as this is one for which a worker today would have no trouble in obtaining compensation. I have referred the patient to a plastic surgeon, who proposes to turn back flaps and make a temporary urethrotomy. The physical and psychological effects of the operation should be entirely satisfactory.

Reviews.

History of the Second World War: United Kingdom Medical Series. Editor-in-Chief, Arthur S. MacNalty, K.C.B., M.D., F.R.C.P., F.R.C.S. "The Emergency Medical Services", by C. L. Dunn, C.I.E., I.M.S. (ret.), with a foreword by the Editor-in-Chief; Volume I; 1952. London: Her Majesty's Stationery Office. 10" × 6¼", pp. 476, with 41 plates and 10 text figures. Price: 50s.

IN THE MEDICAL JOURNAL OF AUSTRALIA of February 28, 1953, a good deal of space was given to a review of a volume entitled "Medicine and Pathology", the first of the "History of the Second World War: United Kingdom Medical Series". "The Emergency Medical Services", Volume I, England and Wales, has been edited by Lieutenant-Colonel E. L. Dunn. The volume is divided into two parts. The first deals with the evolution and operation of the Emergency Medical Services and the second with the ancillary services. Colonel Dunn explains in the preface that the chapters in Part Two have been contributed largely by those who were directly concerned with the events described.

After a short historical review dealing with the period 1923 to March, 1935, the first chapter describes the early steps taken to create a casualty organization during the period March, 1935, to September, 1938. The Emergency Medical Services, as they would have been in September, 1938, if an emergency had occurred, are set out under nine headings, and it is explained that even if an enemy attack had been made by air at that time on the scale experienced in the autumn of 1940, improvised arrangements would have been more or less adequate for most of the casualties. On the other hand, if the scale of attack had been that forecast by the Air Force, arrangements would have been totally inadequate. Between October, 1938, and September, 1939, the Emergency Medical Services were further extended. The result was that at the outbreak of hostilities there were in England and Wales 2370 hospitals—classes IA, IB and II—containing 108,143 beds in the London region, and 384,427 in the provincial regions, a total of 492,570. It was estimated that by "crowding", 136,953 additional beds could have been provided. Lack of space makes it impossible to describe the other steps which had been taken; it must suffice to state that these included arrangements about personnel, aid posts, ambulance trains and so on. By May, 1940, the period of eight months of inaction on the Western Front had given much valuable time for consolidation of the emergency services. There were, on that date, 1207 hospitals with a total of 406,612 beds, and of these, 262,859 were casualty beds. It is explained that certain hospitals were withdrawn, but these included mostly maternity hospitals, homes for incurables, and so on, which would not have been likely to be available for casualties.

The main activities of the Emergency Medical Services are described in three chapters bearing the titles "The Period of Active Operations in Britain, May, 1940, to June, 1941", "Period of Consolidation and Improvement, July, 1941, to December, 1943", and "Period of Active Operations, January, 1944, to End of Hostilities". These chapters have to be read to be appreciated; they are illustrated by a series of striking pictures. In one of the appendices, it is shown that the estimated number of patients admitted to emergency service hospitals for disabilities due to enemy action between 1939 and 1945 was 83,640; of these, 78,100 were civilians, 5220 were civil defence personnel including police, and 3020 were merchant navy personnel including passengers.

The second part of the book is divided into five chapters. These deal with the civil defence services, the ambulance services, medical supplies, the emergency hospital pathological services, the civilian blood transfusion service, radiology, physical medicine, the provision of medical personnel, and the civil nursing service in war time. The civil defence casualty services are discussed under four sections. The first deals with early organization and policy from 1925 to 1939; the second section with the first year of active warfare, 1940 to 1951; the third section with the middle years, 1942 to 1943; and the fourth with renewed heavy raids, flying bombs and long-range rockets from 1944 to 1945. It is interesting to note, in the first of these sections, that when war was declared, the casualty service organization was fairly complete and capable of functioning efficiently, and was not fully manned except in regard to first aid parties. The second, third and fourth sections have many subsections and conclude with the consideration of the lessons learned from the raids. In the chapter on the ambulance services, there is a picture of American ambulances which transported more than 800,000 patients a distance in Great Britain of over sixteen million miles. The problems associated with medical supplies may be gauged from the table in an appendix which sets out quantities of items received as gifts, chiefly from the United States of America. We note *inter alia* that nearly 22,000,000 yards of absorbent gauze were supplied and approximately 6,000,000 blankets. The chapter on the emergency hospital pathological services is by Sir Philip Panton. Among the lessons learned from the working of the pathological services is the pre-war inadequacy of medical laboratories in very many general hospitals. It is pointed out that the establishment of a laboratory in a hospital was often effected against considerable local opposition, but on the other hand, any subsequent suggestion to remove the service or to curtail its activities was eventually even more strenuously resisted. It is stated that the belief that laboratory services are unnecessary to hospital efficiency is not yet entirely dissipated. The chapter on civilian blood transfusion service ends with a general commentary. Three main lessons are stated. The first is that until such time as a safe and equally effective substitute can be discovered, blood transfusion has come to stay and its practice has increased prodigiously and will increase still further. In the second place, the demand can be met provided the appropriate organization is available. Thirdly, blood and blood products are highly dangerous materials, but the dangers can, for the most part, be avoided under constant supervision by highly skilled personnel. The chapter on the provision of medical personnel contains a

wealth of information which it is impossible to summarize. It must suffice to point out that in 1940, the number of medical practitioners in actual practice in peace time in Great Britain and Northern Ireland was found in round figures to be 45,300. Of these, 1400 held regular commissions in the forces. By December, 1940, 7500 additional practitioners had been included in the services. This left 36,400 in civil practice, but of these, 16,700 were over fifty years of age, including about 5000 over seventy, who were either unfit for practice or unlikely to be able to bear the strain of additional work.

This volume is a superb record of organization, courage and endurance. The second volume dealing with the Medical Emergency Services will be anxiously awaited.

Dermatology: Essentials of Diagnosis and Treatment. By Marion B. Sulzberger, M.D., and Jack Wolf, M.D.; Fourth Edition; 1952. Chicago: The Year Book Publishers, Incorporated. 9" x 6¼", pp. 592, with 65 illustrations, some in colour. Price: $10.00.

SULZBERGER AND WOLF'S "Dermatology" is a revised edition of their "Dermatological Therapy", the third edition of which appeared a little over three years ago. In addition to a complete revision of the text, the material has been brought up to date by inclusion of more recent information on dermatological uses of such agents as the newer antibiotics, cortisone *et cetera*.

The first chapter deals with general management of skin diseases, and there then follow sixteen chapters devoted to the essentials of diagnosis and treatment. The book being intended primarily for students and general practitioners, the style is necessarily dogmatic, and there are, therefore, a number of points with which many dermatologists will disagree, for example, the topical use of local anæsthetics in dermatitis. However, the principles enumerated are mainly well tried, and the wisdom of using few remedies and of being thoroughly familiar with their properties is rightly stressed.

The index is comprehensive, and the printing and binding are a credit to the publishers. This book will undoubtedly maintain the popularity of the previous editions, and although the great wealth of detail presented may prove confusing to the average undergraduate, the general practitioner will find it a very handy book for quick reference.

Diseases of the Ear, Nose and Throat: Principles and Practice of Otorhinolaryngology, Clinical Technics and Procedures. By Francis L. Lederer, B.Sc., M.D., F.A.C.S.; Sixth Edition; 1952. Philadelphia: F. A. Davis Company. Sydney: Angus and Robertson, Limited. 10" x 7", pp. 1450, with 979 illustrations, 20 in colour. Price: £10 15s.

THE sixth edition of Lederer's comprehensive text-book (1398 pages) follows the same general pattern as the previous editions, but has been revised, enlarged and brought up to date. Several new chapters are included and others enlarged. Some of the new material has been contributed by the author's colleagues and associates.

There are new chapters on allergy, general pathology, ophthalmology, psychiatry, röntgenology, and one on speech and voice. Other useful new material concerns simulated deafness and malingering and the tests for detection; the rehabilitation of the deaf; electro-diagnosis in facial paralysis; diseases of the salivary glands and ducts; speech therapy and the reeducation of the laryngectomized patient.

As in the earlier editions, the standard of production, of paper, printing, general arrangement of subject matter and illustration, is excellent. The rather large bulk of the book is compensated for by the first-class binding, and the two column set-out of the printing on each page makes for easy reading.

The section on war and its relation to and effects upon the ear is regrettably brief.

The text concerning diverticulum of the pharynx is confusing. The diverticulum is now no longer considered to form at or pass through the posteriorly placed triangular area, where the upper longitudinal muscle fibres of the œsophagus diverge laterally, but to pass through the fibres of the inferior constrictor muscle in the lower part of the hypopharynx, above the stronger, circular fibres at the extreme lower limit of this muscle, which form the so-called crico-pharyngeal sphincter.

In the treatment of laryngeal tuberculosis, a possible criticism is the omission of the use of para-aminosalicylic acid as an adjuvant in the use of streptomycin therapy. A word or two may have been included to say that the older methods of treatment have been largely superseded by the use of streptomycin, even if they were included for the sake of completeness.

In the section on röntgenography of the head, the illustrations of the X-ray photographs are instructive, but it may be that for technique *et cetera* the reader would be better referred to a general text-book of radiology. The brief instructions given could lead the foolhardy to embark on procedures which without adequate training are not without risk.

The chapter on the pathology of tumours of the ear, nose and throat, at the end of the book, is useful for reference, but it should not be regarded as more than an outline and a stimulation to refer to a larger text-book of pathology. The pathology of *keratosis pharyngis* is dismissed in one line: "*Keratosis pharyngis* arises from embryonal cornified epithelial rests." Modern pathologists would doubt the truth of this concept, but no indication is given that there is any doubt. The section is illustrated by 95 photomicrographs.

There is a good index, a feature of which is the inclusion of page numbers in italics to refer to illustrations.

Despite a few criticisms, the book is encyclopædic and is a most valuable compilation, covering every aspect of the speciality of otolaryngology.

A Laboratory Manual of Physiological Chemistry. By D. Wright Wilson; Seventh Edition; 1952. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 9¼" x 6¼", pp. 294. Price: 35s.

THIS is a laboratory manual of biochemistry. Each exercise is adequately described and where necessary any formula required to give a numerical result is provided. There is no discussion of the chemical rationale of the test nor of the physiological significance of any result. It is printed on one side of the paper, but the blanks are numbered. The index is adequate.

Principles and Practice of Obstetrics. Originally by Joseph B. DeLee, M.D., by J. P. Greenhill, M.D.; Tenth Edition; 1951. Philadelphia and London: W. B. Saunders Company. Melbourne: W. W. Ramsay (Surgical) Proprietary, Limited. 10" x 7¼", pp. 1030, with 1140 illustrations, 194 in colour. Price: £5 18s. 9d.

THE tenth edition of DeLee's original "Principles and Practice of Obstetrics" has been practically rewritten by Greenhill, and it now appears under the name of the latter author. It remains an excellent standard text-book, both for students and for practitioners who are interested in obstetrics. The physiology and pathology of pregnancy, labour and the puerperium are thoroughly discussed and the management of normal and abnormal conditions in both mother and child is fully set out. All accepted methods of treatment are considered. The author has enlisted the aid of special authorities in certain subjects, for example, in anæsthesia and analgesia and in the psychological aspect of obstetrics. There is a very good section on obstetric operations and methods of delivery. The use of forceps is excellently illustrated. Much new material has been incorporated in this edition, so that it is a comprehensive and up-to-date work on obstetrics which can be strongly recommended both as a text-book and as a book of reference.

The 1952 Year Book of Drug Therapy (August, 1951-August, 1952). Edited by Harry Beckman, M.D.; 1952. Chicago: The Year Book Publishers, Incorporated. 8" x 5¼", pp. 606, with 114 illustrations. Price: $5.50.

PERHAPS more than any others of the series, this Year Book reflects the changing scene in modern clinical practice. The editor, Harry Beckman, is a pharmacologist and a physician; with his brief but informed comments he keeps in perspective the wide range of material that he has collected from the current literature. A short introduction provides a bird's-eye view of significant developments during the year. The abstracts presented are approached and classified on a clinical basis. Notable in the section on allergy is recent experience with antihistamine drugs and some interesting findings about the action of ACTH and cortisone. A section on antibiotics contains mostly reports on side effects. Cardio-vascular diseases have their own section covering recent experience in the treatment of arrhythmias, congestive heart failure, coronary disease, *cor pulmonale*, endocarditis, hypertension, peripheral vascular disturbances and phlebothrombosis (with a particular emphasis on anticoagulants). The largest section is assigned to internal medicine with subdivisions on chest diseases,

diabetes mellitus, infectious diseases, kidney disturbances, liver disorders, neoplastic diseases, pain, peptic ulcer, poisoning, rheumatic disorders, sprue, thyrotoxicosis, ulcerative colitis and regional enteritis, vitamin deficiencies, and worms and flukes. The material in the sections on surgery and the specialties (dermatology, endocrinology, hæmatology, neuropsychiatry, obstetrics and gynæcology, ophthalmology, oto-rhino-laryngology, pædiatrics and venereology) is selective, but should meet the needs of those interested in a general way; the specialists have their own Year Books. This is a well-prepared volume with a wide appeal.

The 1952 Year Book of Pediatrics (June, 1951-May, 1952). Edited by Sydney S. Gellis, M.D., and Isaac A. Abt, M.D.; 1952. Chicago: The Year Book Publishers. 8" x 5½", pp. 424, with 112 illustrations. Price: $5.50.

THIS Year Book has a new editor, Sydney S. Gellis, with an editorial policy new to the series. Many of the articles abstracted have been submitted to men with special interests in various fields of pædiatrics, and their comments have been reproduced in addition to or instead of the usual editorial notes. This provides a wider and more authoritative expression of opinion than any single editor would hope to offer and, as the amount of editorial material is still kept small, is to be commended. The abstracts are drawn from a wide range of general medical as well as pædiatric literature. They are grouped into sections on the premature and the newborn, nutrition and metabolism, infectious diseases and immunity (with special references to poliomyelitis and tuberculosis), allergy, dentistry and oto-laryngology, ophthalmology, the respiratory, gastro-intestinal and genito-urinary tracts, the heart and blood vessels, blood, endocrinology, orthopædics, dermatology, neurology and psychiatry, therapeutics and toxicology, and miscellaneous subjects. The volume will be useful and acceptable to a wide circle of medical readers.

Advances in Internal Medicine. Edited by William Dock, M.D., and I. Snapper, M.D.; Volume V; 1952. Chicago: The Year Book Publishers, Incorporated. 9" x 6", pp. 464, with 119 illustrations. Price: $10.50.

THIS volume, the latest in the series, contains nine articles, each a monograph in itself. Seven come from medical centres in the United States of America, one from the Netherlands and one from Sweden. Murray H. Bass reviews the effect on the fœtus of some of the more important illnesses affecting the pregnant woman. Richard J. Bing reviews recent advances in catheterization of the heart and great vessels, with particular emphasis on the developments of physiological concepts which have arisen as a result of this technique. A. H. Blakemore discusses portal hypertension and its treatment. G. E. Cartwright and M. M. Wintrobe deal with the subject of the anæmia of infection; their purpose is to summarize, correlate and interpret their own observations, the work of others being reviewed in detail more particularly when it offers additional information. A. B. Gutman and T. F. Yü discuss gout, which they define as a derangement of purine metabolism. R. H. Lyons and V. Logan Love review the clinical aspects of ganglionic and adrenergic blocking agents. J. Mulder, of Leyden, the Netherlands, discusses some aspects of the influenza problem. Charles Ragan describes experiences with ACTH and cortisone. J. Waldenström, of the University of Lund, Sweden, discusses abnormal proteins in myeloma. Each article has a full bibliography, and the volume is completed with author and subject indexes. The book is attractive from the point of view of both its printing and format and its subject matter.

Notes on Books, Current Journals and New Appliances.

Family Doctor. Published monthly by the proprietors, the British Medical Association, Tavistock Square, London, E.C.1. Sole agents for Australia and New Zealand: Gordon and Gotch (Australia), Limited. Subscription for twelve months: 20s. (sterling), including postage.

It is difficult to imagine a parent who would fail to find interest and help in the April issue of this popular medical monthly. Sound and readable articles deal with the first ten minutes of a baby's life, keeping children safe from accidents, the creative impulse in play, feeding the one-year-old, and understanding the adolescent boy. Subjects of more general interest include smoking and its possible harmful effects, viruses, eyes, the control of tuberculosis, "blackouts", toothpastes, rheumatism, sore throats, keeping good health, choosing shoes, light diets (a detailed, practical discussion for the home cook) and many smaller features. This issue is as attractively produced as ever with lots of pleasing illustrations. It can be strongly recommended, especially for more thoughtful parents.

Books Received.

[*The mention of a book in this column does not imply that no review will appear in a subsequent issue.*]

"Clinical Allergy", by French K. Hansel, M.D., M.S.; 1953. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 10" x 7", pp. 1006, with 86 illustrations and three plates in colour. Price: £9 3s. 9d.

This volume is presented as a complete text on the subject of general allergy, replacing the author's "Allergy of the Nose and Paranasal Sinuses", published in 1936.

"Practical Dermatology: For Medical Students and General Practitioners", by George M. Lewis, M.D., F.A.C.P.; 1952. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 10" x 6½", pp. 338, with 99 illustrations. Price: £3 11s. 3d.

Has been designed as a text for medical students, a practical guide for practitioners and an aid in orientation for other specialists.

"Nutrition and Diet: In Health and Disease", by James S. McLester, M.D., and William J. Darby, M.D., Ph.D.; Sixth Edition; 1952. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. 9¾" x 6¼", pp. 722, with 14 text figures. Price: £4 15s.

Intended to provide the reader with "a modernized version of the subject matter" formerly covered in previous editions which appeared in 1927, 1931, 1939, 1943 and 1949.

"Transactions of the Fifth American Congress on Obstetrics and Gynecology", edited by George W. Kosmak, M.D.; 1952. Sponsored by the American Committee on Maternal Welfare, Inc. Held in Cincinnati, Ohio, March 31-April 4, 1952. Published as a supplementary volume to the *American Journal of Obstetrics and Gynecology*, Volume 64A, December, 1952. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 10½" x 7", pp. 616, with 39 illustrations. Price: £6 11s. 3d.

Gives a full account of the Congress with lists of office-bearers *et cetera*.

"Fibrocystic Disease of the Pancreas: A Congenital Disorder of Mucus Production—Mucosis", edited by Martin Bodian, M.D.; 1952. London: William Heinemann (Medical Books), Limited. 10" x 7¼", pp. 254, with 133 illustrations. Price: 63s.

A monograph based on 116 case reports, with biochemical, bacteriological and hæmatological data.

"Reason and Unreason in Psychological Medicine", by E. B. Strauss, M.A., D.M. (Oxon.), F.R.C.P., with a foreword by Russell Brain, M.A., D.M. (Oxon.), F.R.C.P.; 1953. London: H. K. Lewis and Company, Limited. 8½" x 5", pp. 68. Price: 8s. 6d.

Consists of three lectures in which the author considers the principle of causality in psychiatry.

"Practice of Psychiatry", by William S. Sadler, M.D., F.A.P.A.; 1953. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 10" x 7", pp. 1184. Price: £7 17s. 6d.

The purpose of the book is "to serve as a ready and compact reference for diagnosis and immediate treatment".

"The Medical Clinics of North America"; 1952. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. Philadelphia Number. 9" x 6", pp. 372, with 50 illustrations. Price: £7 5s. per year in cloth binding and £6 per year in paper binding.

This is a "Philadelphia Number", a symposium on pædiatrics, consisting of twenty-nine contributions, by thirty contributors.

The Medical Journal of Australia

SATURDAY, MAY 9, 1953.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: surname of author, initials of author, year, full title of article, name of journal without abbreviation, volume, number of first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

AMERICAN LIGHT ON VOLUNTARY HEALTH INSURANCE.

THE first full and clear indication to the medical profession of his design for a National Health Service was given by Sir Earle Page, Minister for Health, in an address to the Federal Council at Brisbane in May, 1950, just prior to the Australasian Medical Congress held in that city. The Minister's address may be found in THE MEDICAL JOURNAL OF AUSTRALIA of July 8, 1950, at page 55. What the Minister presented was a scheme for the subsidization by the Government of voluntary contributory medical insurance. The Minister made it clear that the essential point of his scheme was the acceptance by the individual of some responsibility with regard to the maintenance of his health. This psychologically sound idea met with the instant approval of the members of the medical profession and they decided to give full cooperation in a plan in which this was included. A great deal has happened since May, 1950, and many discussions have taken place between the Minister and the Federal Council on the one hand and the Branches of the British Medical Association and their members on the other. The Government, with the approval and cooperation of the profession, has made considerable progress in its health legislation. It has, as we all know, introduced a system of hospital benefits in which a certain amount of money is paid to each hospital in respect of every patient admitted for treatment. It has introduced a pensioner medical service and also has inaugurated a scheme by which expensive and what have become known as "life-saving" drugs are supplied to the patient without any direct charge being made to him. For the sake of completeness the payments to sufferers from tuberculosis and the supply of free milk to school children should be mentioned. The details of the plan for a National Health Service should be known to everyone because of the pamphlet recently issued by the Minister in which the whole matter was clearly described. The object of the medical benefits scheme is described in this pamphlet as an attempt to insure that everyone in Australia who makes provision through insurance will be able to cover the major cost of all surgical and medical attention whenever and wherever sickness or accidents occur. A bill covering the provision of Pharmaceutical Sickness and Hospital Benefits and the provision of Medical and Dental Services was brought down by the Minister to the House of Representatives just before the end of the last session. Unfortunately, debate was postponed and will not be resumed until the House sits again in September next. In the meatime, the National Health Service is due to come into action on July 1, 1953.

Voluntary insurance, to be really effective in a community, must be undertaken by a large number of people. To many members of the community the idea is new; they have to be made to see that the idea is good, in other words, insurance has to be "sold" to them. During one of his visits to the United States, Sir Earle Page learned of the enormous progress which had been made in that country by voluntary organizations in the matter of hospital and medical insurance. He conceived the splendid idea of bringing two of those who had helped to achieve success in America to visit Australia at the invitation of the Commonwealth Government to explain to all and sundry how the insurance ventures started in the United States and how progress, of great surprise to some and inspiration to others, has been made over a period of twenty years. The two visitors were Mr. E. A. van Steenwyk, Director of the Philadelphia Blue Cross and an official delegate of the Blue Cross Commission of the American Hospital Association, and Mr. William S. McNary, Executive Vice-President and General Manager of the Michigan Blue Cross and official delegate of the Blue Cross Commission of the American Hospital Association. These gentlemen were introduced to the public of Australia at a dinner given by the Commonwealth Government at the Hotel Australia, Sydney, on April 15, 1953. The dinner was attended by representatives of medical, hospital and pharmaceutical organizations and of other bodies concerned with insurance, social service and so on. It should be explained that Blue Cross has to do with hospital service and Blue Shield with medical service to patients in hospital. Beginning with the fundamental statement that every nation had to recognize the provision of medical benefits and hospital benefits to members of the community as a social problem, these American observers told in most interesting fashion the story of the development in the United States of Blue Cross and Blue Shield. Twenty years ago, when the work of Blue Cross was started by a few ardent souls, many people, especially those in high places, doubted whether real success would be achieved. At the end of the first year's work, when something like a membership of one million was reported, those in charge of the work were given to understand by authorities in Washington that that was about as far as they were likely to go, that people could never be persuaded to insure themselves in any great numbers. At the end of the next year, membership was three million, and again those in high places smiled and found some

explanation other than the real one for what had been achieved. When the depression came, organizers were given gloomier and gloomier forecasts, but the membership still rose, and before long ten million people had joined. When the second World War broke out, it was said that a nation at war would not be inclined to take voluntary insurance for hospital care, but still the membership continued to rise. At the present time something like forty-four million people in the United States and Canada are insured for hospital benefits. This number, it was pointed out, is equal to the population of England and Wales. Twenty years ago, the equivalent of £3000 was paid in one year to American hospitals by Blue Cross, but now the amount is something like £300,000,000 a year. We all know that nothing succeeds like success, and we can well understand the altered attitude of hospital authorities whose first conceptions of the venture were anything but encouraging. When they saw that sums of money which became larger every year were being paid to them, they became enthusiastic and wanted to further the scheme to the best of their ability. Mr. van Steenwyk spoke of the money that was paid to hospitals under Blue Cross and to medical practitioners under Blue Shield as "new money", thereby implying that a great deal of this money would not have been forthcoming except for the existence of these two organizations. He said that this was one of the most important considerations in connexion with voluntary insurance. Another point made by him was that according to Blue Cross and Blue Shield the patient was allowed to choose his own hospital and his own doctor. This acted in such a way that hospital services were kept at a high standard. People did not willingly seek treatment in hospitals which were dirty and had "bum doctors and sour nurses". These hospitals would find that the payments from Blue Cross failed to be made and they would before long discover the reason why. Mr. van Steenwyk also insisted that such organizations as Blue Cross and Blue Shield should be non-profit-making. Reference was made to the expense rate of the American organization. Sir Earle Page pointed out that the expense rate was only 8%; in other words 92% of the premiums went back to the contributors. He raised more than a smile on the faces of those present when he remarked: "That will be the day when 92% of the Government taxes go back in direct services to the people." Of course, the expense rate was not always as low as 8%. Mr. McNary described how it had come down from 25% and 20%, and how in some cases it had become less than 5%. Two important points emerged from the discussion, and they deal with matters which have caused some concern to practitioners in this country. They were discussed at some length when Mr. van Steenwyk and Mr. McNary addressed members of the New South Wales Branch at a meeting specially called for the purpose. These questions had to do with preexisting disease and the inclusion of elderly persons. The speakers explained that in America preexisting disease was disregarded—a diabetic or an asthmatic person was accepted just as readily as those who did not suffer from these complaints. In any case, as Mr. van Steenwyk put it, the whole matter would work itself out in the course of time. A person who was admitted to the scheme today as free from preexisting disease was very likely to be suffering from one of the diseases in question after a period of ten years, when he would still be a member of the scheme and would be carried on in the normal way. The same applied to persons of advanced years. A man who was admitted at fifty years of age would after a period of ten years be carried on in spite of his age, and in America it was thought that the risk might just as well be taken at the start. Neither Blue Shield nor Blue Cross rejected people on account of preexisting disease or advanced years and no difficulty had been experienced on this account.

The workings of the American Blue Cross and Blue Shield might be discussed in much greater detail, but this is not necessary for the present purpose. What is needed is to show that schemes of voluntary insurance in the matter of hospital and medical benefits do work. In America they have been initiated and carried on in spite of an apathetic and non-cooperative Government. In Australia the position of affairs is reversed. Mr. van Steenwyk put the matter clearly when he said: "In Australia a new chapter in the history of health insurance is being written. For the first time a sympathetic Government under the leadership of its Minister for Health has devised a scheme in which the Government and the people will together work out the medical expense problem, leaving the matter of selection of hospital and doctor entirely up to the people served." All along the Minister has declared, as already pointed out, that self-help is of the utmost importance. It is a matter of everyday experience that people who do things for themselves are much stronger in every way than people who have something done for them. They are certainly more appreciative of the result when it has been obtained. We can also say without fear of contradiction that what has been done in the United States and Canada can be done in Australia, especially when conditions are more favourable for the doing of it. In the proposed National Health Service of the present Australian Government, the medical profession has no executive part to play, beyond the fact that it must maintain at all times the highest quality of service in hospitals, in the consulting room and in the homes of the people.

Current Comment.

THE CONTROL OF BOWEL EMPTYING.

"THE rehabilitation of patients totally paralysed below the waist, with special reference to making them ambulatory and capable of earning their own living", is an ambitious subject for discussion. However, an article by Donald Munro[1] on the control of bowel emptying, one of a series on this general subject, makes a very practical contribution to the solution of the problem. Munro, as assistant professor of neurosurgery in the Harvard Medical School, associate professor of neurosurgery in the Boston University School of Medicine and surgeon-in-chief in the department of neurosurgery of the Boston City Hospital, writes with some authority. He first of all reviews the neurophysiological and practical aspects of the control of bowel emptying in the normal person. Going on to describe the extensive clinical material on which his experience is based, Munro states that cord lesions affecting the lumbo-sacral part of the cord were those most likely to produce abnormal bowel reactions, with those of the thoraco-lumbar part of the cord

[1] *New England J. Med.*, January 8, 1953.

next. However, spinal shock (by its influence on all reflex activity) played at least as great a role in the production of gastro-intestinal areflexia and paralysis as either the level or the type of cord injury. Referring to treatment in the acute stage, Munro states that while spinal shock is present and the abdomen remains silent, the patient is given no food or fluid, including water, by mouth. A rectal tube is inserted and left in place for one out of every two hours. If vomiting occurs, Wangensteen suction is instituted. Bladder distension is controlled by tidal drainage. When peristalsis is again audible and there is no further dilatation of the stomach, administration of fluids is started, followed by gruel in small amounts (60 to 120 millilitres) at frequent intervals (every one or two hours). This diet is increased gradually until the patient is taking by mouth a mixed diet containing 3000 Calories. In the intermittent stage, with the return to a normal diet and for as long a period as the bladder remains atonic or hypertonic or is not reflex in its activity as determined by repeated cystometrograms, the bowels are controlled by soapsuds, oil-retention or milk and molasses enemas supplemented by manual extraction of any impacted fæces. With the evidence, as provided by the demonstration of a reflex bladder, that segmental reinnervation of the bowel is again established, institution of bowel training can be started. The final and most important precedent to bowel training is that the anal reflex must be active. Bowel training depends upon the establishment of a conditioned spinal bowel reflex. As the first step in conditioning the necessary reflexes a soapsuds enema is self-administered by the patient every morning at some previously chosen time, which will thereafter be unalterable. The enema should be as small as is compatible to ensure emptying of the bowel. The patient does best if he is seated on the toilet, next best on a commode and worst on a bedpan. Efforts should be made, therefore, to mobilize him sufficiently to make it possible for him to use a toilet. After a week of this bowel routine, the enema should be omitted every third day, and a dose of milk of magnesia, given by mouth, should be substituted for it. The dose should be just large enough to ensure a bowel movement. After this routine has been established, the remaining enemas are gradually eliminated one by one, milk of magnesia by mouth being substituted for each. Thus, reflex emptying of the bowel has been conditioned first as to the time between evacuations, secondly as to the stimulus of the rectum locally by the enemas, and thirdly as to stimulation of the large bowel peristalsis generally by the milk of magnesia. Mineral oil is given in addition throughout this period in order that the fæcal mass may be maintained in the proper soft solid consistency. The final step in bowel training is to eliminate the milk of magnesia. This is done by gradual regular periodic withdrawal. This final step eliminates all conditioning stimuli except the temporal one.

Munro states that bowel training as described has been carried out on 42 of 310 patients with spinal cord lesions. He considers that there can be no doubt that a conditioned reflex that will permanently regulate bowel discharge can be established in the absence of all somatic neural connexions between the brain and the spinal cord and without the need for enemas, suppositories, catharsis or digital stimulation. If the patient who has been educated in the way described will continue to go to stool every day or every other day at the time he has already chosen and conditioned his bowel to move at, he can be sure that, barring intestinal upset or disease, his bowel will empty itself at the designated time and at no other time.

THE BALLISTOCARDIOGRAM.

"ANY bright boy with a knowledge of how to work in a machine shop and put together a radio could build himself a ballistocardiograph. . . ." Thus Isaac Starr[1] starts an account of the different types of instruments used to record the movement of the body due to cardiac action, in what he calls a critical essay on the "Present Status of the Ballistocardiogram". This is a good review of the subject with an extensive bibliography: a timely review, too, because of the increasing interest being taken in this method of investigating cardiac function since the introduction of portable machines. Another good recent review is given by Edward Rubenstein.[1] The original instruments were of the moving table type. The subject lies at rest on one of these specially constructed tables and the rhythmic movement of the table caused by the pumping action of the heart is magnified and recorded. It is usual for this movement to be recorded in the longitudinal direction with the subject horizontal, but ballistocardiograms have also been designed to record ballistic forces in other directions—for example, vertically with the subject sitting or standing. Some of the newer models are designed to record movement not simply in terms of distance of displacement, but in terms of velocity and of acceleration. Portable instruments are not so accurate, but it is quite remarkable how similar are the ballistocardiograms taken by various types of machines. The portable instrument in most general use consists of a bar which rests across the shins of a subject lying supine on a rigid table and a device placed on the table for recording the movement of the bar. Electrocardiographic equipment can be used to give a tracing of the record. The important thing, however, is to know what the curves mean, and advances in this knowledge have been slower than the improvements in technique. When the heart ejects blood up the aorta, the body recoils footwards, and this recoil is recorded in the ballistocardiogram. When the ejected blood strikes the arch of the aorta, the shock causes the body to move headwards. Later, when the blood bumps up against the resistance of the peripheral small arterioles, the body is moved footwards again. These are some of the simpler factors involved. In the early days of ballistocardiography it was hoped that a simple measure of cardiac output had been found. Starr developed formulæ for deriving output from the amplitude of the ballistic curves, and J. M. Tanner[2] has suggested a modification of the formula to bring the results into line with Cournand's catheter studies. In general, the curves are bigger when cardiac output is increased, as in exercise, but other factors also affect amplitude, such as the strength of cardiac action: a small amount of blood ejected very forcibly may move the body to the same extent as a large volume of blood ejected more slowly. Then again, the elasticity of the large arteries, the state of dilatation or constriction of vessels, and the extent to which the fascial, fatty and other layers of the body absorb the movement without transmitting it to the table affect the recording. It is this multiplicity of factors affecting the ballistics of the body which is the weakness of present-day ballistocardiography. It is the recognition of this that has driven the ballistocardiograph from the scientific level to the empirical clinical field, and even here it is on uncertain ground. Abnormal curves have been described in a variety of cardio-vascular diseases, but the type of abnormality is often inconstant in any particular disease and adds nothing to precision of diagnosis that cannot be achieved more easily by other means. Its greatest usefulness is said to be in detecting cardiac abnormalities in patients with *angina pectoris*. There is no doubt that the ballistocardiogram has led to a better understanding of some aspects of cardiac activity and that more can be expected from it in the future. All reviewers refer to its being in its infancy. At present the tendency is to try to extract precise information about the heart from the pattern of a curve which depends on a number of variable factors, rather a hopeless task unless we know what all these factors are and can control or measure by other means the more important of them. It has many experimental hurdles to pass over. In the meantime the clinician would do well not to overrate his or anyone else's ability to interpret its curves—and not to expect a rather backward child to do a man's job. The "bright boys" should continue to build machines and to do research.

[1] *Ann. Int. Med.*, November, 1952.

[1] *New England J. Med.*, July 31, 1952.

[2] *J. Clin. Investigation*, May, 1949.

Abstracts from Medical Literature.

OPHTHALMOLOGY.

The Neuro-Vascular Mechanism in Congenital Glaucoma.

E. SCHMERL AND B. STEINBERG (*Am. J. Ophth.*, May, 1952) investigated the role of neuro-vascular mechanism in cases of congenital glaucoma in adult rabbits and in their descendants. Experiments on six rabbits with congenital glaucoma indicated that the disease was associated with a faulty secretion of pituitary principles with an increased quantity of hyperpiesin. Descendants of these rabbits with congenital glaucoma were examined for signs of glaucoma, but none were found. They were subjected to various experiments from which the authors were able to conclude that there was evidence of dysfunction of the neuro-vascular mechanism and that diencephalic centres failed to regulate the stability of the intraocular pressure. The descendants also showed abnormality in the secretion of pituitary principles. These findings indicate that instability of intraocular pressure exists in the absence of such factors as malformation of the filtration angle, small eyes, and large lenses.

Treatment of Retrolental Fibroplasia.

WILLIAM O. LAMOTTE *et alii* (*Arch. Ophth.*, May, 1952) present observations made during the treatment of 17 premature infants with vitamin *E* and of 21 premature infants with ACTH and cortisone. The disease was in an active phase when treatment was commenced, except in two cases in which membrane formation was complete and in 10 in which the process developed while the infants were receiving prophylactic vitamin *E* therapy. The results of therapy with vitamin *E* were very discouraging. In 10 of the 17 cases the disease developed while prophylactic vitamin *E* therapy was being administered. Of the remaining eight patients three will have some degree of useful vision in one eye, and five have normal or apparently normal vision in one or both eyes. Treatment with ACTH or cortisone was also disappointing. Nine of the 21 patients treated became blind in both eyes, three were blind in one eye and had impaired vision in the other eye, and nine had normal vision in one or both eyes. Undesirable side effects noted with ACTH were fluid retention, increased appetite, increased susceptibility to infection, rounding of facial contours and pustular dermatitis.

Subclinical Retinal Detachments.

C. L. SCHEPENS (*Arch. Ophth.*, May, 1952) defines a subclinical detachment as one in which the diagnosis cannot generally be made with the usual methods of investigation. The detachment is so flat or so peripheral or both that it escapes notice unless a careful and methodical ophthalmoscopic examination is performed under the best possible conditions. A very flat and peripheral detachment may be diagnosed if attention is paid to the following signs: the choroidal pattern appears ill-defined and hazy over the region of the detachment, and the retinal vessels cast a visible shadow on the choroid. The detached retina often shows abnormal water-silk-like reflections. There are three types of cases which require more than direct ophthalmoscopy for diagnosis: cases in which the subclinical detachment is hidden by a fine vitreous haze in the fundus periphery, cases in which the subclinical detachment is so peripheral that it cannot possibly be seen by direct ophthalmoscopy and cases in which diagnosis cannot be made without indenting the sclera. The author divides subclinical detachments into two types, one in which there is a visible retinal break but only a small and extremely peripheral detachment, and the second in which there is a retinal break and a detachment so small that it may be difficult to detect. The author discusses the subjective symptoms and the signs in 102 patients with subclinical detachment. Thirty-nine patients were subjected to operation with success in 38. The indications for operation are not clear, but vitreous hæmorrhage and sudden appearance of localized flashes of light are considered signs of activity and are indications for operation.

Evaluation of Local Cortisone Therapy in Ophthalmology.

M. FINE AND R. C. GOODWIN (*Arch. Ophth.*, June, 1952) record their results in 121 patients with ocular disease who have been treated with cortisone by local administration. Two patients with severe allergic conjunctivitis associated with contact dermatitis responded dramatically to local cortisone therapy. Of corneal lesions treated, cortisone had a dramatic effect on marginal corneal ulcers, no effect on dendritic keratitis, but beneficial effect on disciform keratitis and metaherpetic keratitis. The authors found that a possible hazard in the use of cortisone is the activation of herpes virus by cortisone. Non-syphilitic keratitis responded promptly to treatment. A small group of corneal degenerations treated showed no response. Cases of anterior uveitis responded most favourably to local cortisone therapy. In chronic uveitis there was no response to cortisone. Diseases of the choroid and retina showed no response to therapy. Sympathetic ophthalmia and post-operative inflammation responded effectively.

ACTH in the Treatment of Retrolental Fibroplasia.

A. B. REESE *et alii* (*Arch. Ophth.*, May, 1952) present the results of treatment of retrolental fibroplasia with ACTH. For the purpose of records they have divided the disease into five stages: Stage 1—tortuosity of retinal vessels *plus* neovascularization, which is usually seen in the extreme periphery of the fundus. Stage 2—stage 1 *plus* peripheral œdema and vascular dilatation; spontaneous regression may occur in this stage. Stage 3—stage 2 *plus* a large amount of œdema and retinal detachment in the periphery of the visible fundus; spontaneous regression is unlikely. Stage 4—hemispherical or circumferential retinal detachment. Stage 5—complete retinal detachment. For any treatment to be successful it must be commenced in the first three stages. The duration of treatment varied from nine to thirty-three days, and the dosage administered varied from 72 to 1235 milligrammes. The average daily dose was 15 milligrammes per kilogram of body weight per day. Fundi were examined three times per week. Under treatment the infants have a ravenous appetite, are irritable and show inhibition of growth. Of 36 infants treated six died and seven had severe infections. Of 49 infants not under treatment one died and one had an infection. The authors believe that the treatment was responsible, in part at least, for the mortality and morbidity. There were no deaths when duration of treatment was only two weeks. The end phase of the disease was divided into five grades: Grade 1—pale fundus with attenuated vessels. Grade 2—grade 1 *plus* a small mass of opaque tissue in the periphery with or without visible small retinal detachment. Grade 3—a large mass of opaque tissue in the periphery incorporating a retinal fold which extends to the disk. Grade 4—retrolental tissue covering part of the pupillary area. Grade 5—retrolental tissue covering the whole of the pupillary area; no red reflex. The outcome was considered satisfactory if the disease was stopped in grade 1 or 2. When all cases treated and untreated were analysed, it was found that there was no significant difference. The authors conclude that ACTH has no effect on the course of the disease, and they have discontinued its use.

An Operation for Congenital Glaucoma.

J. LAVAL (*Am. J. Ophth.*, July, 1952) performs goniotomy *ab externo* combined with iris inclusion for congenital glaucoma so that drainage will occur in cases in which the canal of Schlemm has become occluded. The technique is simple; a conjunctival incision is made seven millimetres from the limbus over one-third of the circumference of the globe and the flap reflected to the limbus. A scratch incision is then made in the sclera two millimetres behind the limbus, and this extends for about one-third of the circumference of the globe. An iris repositor is then inserted into the anterior chamber and is swept up and down. The iris then is withdrawn through the wound at the upper temporal portion and cut half-way across allowing one pillar to lie on the sclera. The conjunctival flap is closed by a running suture. The eyes heal quickly and there is no reaction.

Narrow-Angle Glaucoma.

P. A. CHANDLER (*Arch. Ophth.*, June, 1952) discusses narrow-angle glaucoma, its differences from wide-angle glaucoma, and its treatment. He states that in narrow-angle glaucoma the obstruction to outflow from the anterior chamber is due solely to block of the angle by contact between the periphery of the iris and the trabeculum. The closure of the angle may be temporary and reversible, or permanent, because of peripheral anterior synechiæ. In narrow-angle glaucoma, whenever the angle is fully open the tension is normal. In wide-angle glaucoma, since the angle is always fully open, aqueous has free access to the angle, and obstruction to outflow is due to a primary abnormality of the filtration apparatus. In discussing the mechanism of an acute rise in tension in eyes predisposed because of a shallow anterior chamber, the author favours relative pupillary block as the principal mechanism. In discussing treatment the author is of the opinion that if acute narrow-angle glaucoma does not respond to miotics after two or three hours, then surgery should be resorted

to. He is of the opinion that a trial of six to twelve hours without substantial lowering of the tension is unjustified. For surgical treatment in early cases or cases in which tension returns to normal with miotics the author recommends peripheral iridectomy or iridotomy. He considers that in an acute attack which has been controlled peripheral iridectomy should be performed except in the elderly. Young people who have had an acute attack in one eye should have a prophylactic peripheral iridectomy in the other eye. For subacute or chronic narrow-angle glaucoma in which the angle is closed by peripheral anterior synechiæ, the author recommends iridencleisis or peripheral iridectomy combined with cyclodialysis. Cyclodialysis without iridectomy is not recommended for any stage of narrow-angle glaucoma.

OTO-RHINO-LARYNGOLOGY.

Allergy of Upper Respiratory Tract.

M. F. JONES (*Arch. Otolaryng.*, March, 1952) states that an acceptable arrangement for the treatment of allergic patients is to combine the efforts of the allergist and the otolaryngologist. The following programme is proposed: (i) daily outdoor exercise; (ii) establishment of controlled emotional balance in proportional living; (iii) adjustment of damaging irregular living habits; (iv) elimination of contacts with known allergic irritants; (v) desensitization to dusts and moulds and to histamine; (vi) selection of a nutritionally complete allergen-low dust; (vii) application of skin tests with appropriate treatment of seasonal allergies; (viii) administration of antihistamines for treatment and diagnosis where indicated; (ix) correction of organic irregularities; (x) doing the necessary surgery in carefully selected cases. The author goes on to state that desensitization by the minimal dose method against dust, moulds and histamine has proved to be satisfactory. The reactions to skin tests with very fine dilutions are used in the selection of the most desirable dilutions with which to start treatment. Patients thought to be highly sensitive receive an intracutaneous test with 0·05 millilitre of a 1:1,000,000,000 dilution of histamine phosphate. Three days later 0·1 millilitre is injected subcutaneously. Treatments are given twice a week, the amount increasing 0·1 millilitre with each dose until 0·5 millilitre has been reached. For the next series of injections 1:100,000,000 dilution may be similarly employed. Further treatment is not administered when definite improvement is evident. Immediate improvement may occur after the first test dose, in which case further treatment is not considered. Further treatment after improvement is observed may impair the results gained. Skin testing for foods has proved to be misleading. A clinical method of testing is preferred. Foods are selected because of their low incidence as clinical disturbers, while those which commonly cause symptoms are avoided. The most frequent offenders are milk and milk products, wheat products, eggs, shellfish, chocolate and nuts. Unfortunately the most valuable proteins are contained in milk, eggs and meat. Of the three, meat causes less trouble; so with elimination of milk and eggs, meat with its natural fat is allowed as the basis of diet. Pork and beef are the commonest symptom-producing meats; so that if either is suspected, fish or fowl meat may be ordered during the test period. By a process of adding single additional test foods to the diet and watching for symptoms, offending foods may be detected and avoided. In a group of five patients with polypoid nasal changes and the common associated symptoms, essential surgical procedures were carried out, and at the same time anti-allergic measures were given including desensitizing injections against dust and histamine. This combined attack produced relief in all five cases which neither surgery nor desensitizing procedures had brought about when previously tried alone.

Topical Anæsthesia in Bronchoscopy.

H. J. RUBIN AND B. M. KULLY (*Arch. Otolaryng.*, July, 1952) state that the commonly used topical anæsthetics, cocaine and tetracaine, are each the subject of occasional case reports describing toxic reactions. Consideration has not always been given to avoidance of reactions due to hypersensitivity. Toxic reactions to these drugs are due to overdosage, hypersensitivity or too rapid administration. Overdosage is the chief cause of reactions. Close attention to the total dose by actual measurement, as well as to speed of administration and preliminary testing for sensitivity, would greatly reduce severe reactions and deaths. The commonly recommended maximum dosage of tetracaine and of cocaine, based upon animal tests of toxicity, is too small for the needs of topical anæsthesia for bronchoscopy and is too far below what the human organism will safely tolerate. For several years a dose of 50 milligrammes of tetracaine (that is, 10 millilitres of 0·5% solution) has been used on all adults without incident. With cocaine 300 milligrammes (that is, six millilitres of 5% solution) may be employed. These amounts are never exceeded in any patient. In experimenting with rabbits, it was found that with topical applications there was no difference in toxicity of various concentrations, the minimum lethal dose being the same regardless of concentration. The only important factor was total dose of drug. Those who do not measure the amount of anæsthetic used are more likely to exceed the safe dosage. It has been demonstrated in rabbits that with overspeedy instillation much of the solution may run into the alveoli, where absorption is rapid, so that minimal lethal doses may be decreased with rapid administration. In practice fractional application over a period of ten minutes affords adequate protection and allows time for a possible hypersensitive reaction to occur before the entire amount has been given. Hypersensitivity may be safely tested for by permitting the patient to use a small measured amount of the anæsthetic in lesser concentration than that later to be used in the tracheo-bronchial tree (that is, five millilitres of a 1% solution of cocaine or four millilitres of a 0·25% solution of tetracaine). If a patient tolerates these test amounts, he is able to take the additional calculated amount needed for complete anæsthesia. Epinephrine, if administered rapidly, may actually increase the toxicity of tetracaine or cocaine. In no instance was it found to lessen the toxicity of cocaine, but it does appear to afford some additional protection with tetracaine. Epinephrine is not used at all in the author's practice. Application of the anæsthetizing solutions, after the preliminary gargling, is made drop by drop, the surgeon using a syringe with a suitable applicator, being guided by a laryngeal mirror, and lateral posturing of the patient, especially to reach the left lung.

Acoustic Neurinoma.

E. H. ROCKOWITZ AND G. G. LERNER (*Arch. Otolaryng.*, October, 1952) state that 8% of all intracranial tumours are acoustic neurinomata. Some believe that the tumours arise from embryonic glial tissue, others are of the opinion that they originate from the cells of the sheath of Schwann and should be called Schwannomata or neurinomata. In the majority of cases the tumour springs from the vestibular portion of the eighth nerve within the internal auditory meatus. Small tumours may exist without producing symptoms. They are very slow-growing. The first and foremost symptoms are deafness and tinnitus. Only later in the disease does one find attacks of vertigo. It is thought that, with the slow growth, vestibular compensation has time to take place, while irritation of the cochlear division immediately presents itself as tinnitus and progressive deafness. The type of deafness is of special interest. There may often be a low tone loss in the earlier stages rather than the typical nerve type of curve. Later in the disease typical nerve deafness may become manifest. Attempts have been made to explain this happening on anatomical grounds, the lower tone conducting fibres tending to be in the centre of the nerve and thus more liable to pressure atrophy then the more peripherally placed high tone fibres. The semicircular canals may be found to be hypoactive or completely inactive on the affected side. Contralaterally the vertical canals may be inactive, hypoactive or perverted, while the horizontal canals may show either normal or perverted responses. Classically there is a dead labyrinth on the diseased side with impairment of vertical canals on the opposite side. As a rule the degree of vestibular disturbance parallels the size of the lesion. A peripheral facial paralysis of the affected side may occur later in the disease. With growth mesially of the tumour the patient may complain of neuralgic pains, or there may be areas of anæsthesia corresponding to the distribution of the first division of the fifth nerve. Loss of corneal reflex and disturbance of the muscles of mastication on the side of the lesion may result from further extension. Symptoms referable to the sixth, ninth and tenth nerves may develop, and pressure on the cerebellum may produce symptoms of cerebellar dysfunction. Papilloedema and signs of increased intracranial pressure may follow. A case is described in which deafness and tinnitus developed after pregnancy. There were right occipital headaches and constant giddiness. An audiogram revealed a right-sided nerve-type of deafness. There was no response from caloric stimulation of the right ear. The cerebro-spinal fluid examination gave normal results on the right side. An acoustic neurinoma was successfully removed from the right internal auditory meatus.

Special Articles for the Clinician.

(CONTRIBUTED BY REQUEST.)

LXII.
PILES OR HÆMORRHOIDS.

THE origin of the word "pile" or "piles" is obscure. The synonomous word, "hæmorrhoids", is derived from the Greek and was first used in its medical sense by Hippocrates, prior to whose time all lesions in the region of the anus were called hæmorrhoids. Famous sufferers from piles included Don John of Austria and Martin Luther.

Internal Piles.

Internal piles or hæmorrhoids are the commonest of all rectal complaints and are often referred to as "bleeding piles". They are almost confined to adults, men are affected more often than women, and they are often hereditary.

The symptoms of internal piles are bleeding and prolapse. The bleeding is painless, bright like nose-bleeding and not incorporated in the motion. It occurs with stool or immediately afterwards, and often in spurts, which spatter the sides of the pan. The bleeding is usually frank and distinct; blood that is merely smears on the toilet paper is more likely to be due to anal fissure, pruritus and skin tags than piles. Prolapse of the piles may occur with stool or during exertion or exercise. They may return naturally or require manual replacement. In the later stages they are permanently prolapsed.

The source of rectal bleeding is often elusive and its investigation demands a careful history, interrogation and examination.

During the general examination and interrogation of the patient, one should seek for evidence of diverticulitis, cirrhosis of the liver, anæmia, enlargement of the prostate and carcinoma of the large bowel. Carcinoma of the rectum must be specifically excluded. Such patients usually suffer from diarrhœa rather than constipation, and any patient complaining of piles with a history over several months of the frequent passage of blood and mucus must on the history alone be regarded as a cancer suspect. Beware also of the patient with the history of something in the bowel which he cannot pass. Both piles and carcinoma are often present in the same patient.

On external examination of the anal region, any abnormalities should be noted, such as skin tags, prolapsing piles, the openings of fistulæ, the grey sodden skin of pruritus, the spasmodic contraction of an anal fissure, or the lax anus of prolapse. Thrombosed external piles appear as firm swellings, often bluish in appearance, at the anal margin, whilst it is often easier to palpate the track of a fistula than to see its opening. Prolapsing piles may be visible at the anal margin or be brought down by a cough.

Although internal piles themselves are not palpable, digital examination of the rectum is one of the most important steps in the examination. About 60% of all carcinomata of the large bowel are in the region of the recto-sigmoidal junction and within reach of the examining finger. The little spot of fæcal matter which so often adheres to the tip of the glove when the finger is withdrawn should be carefully examined for any sign of adherent or admixed dark blood, or be smeared on a piece of filter paper and examined by the guaiacum test. The finding of dark blood in this way is presumptive evidence of carcinoma of the rectum until excluded.

By proctoscopic examination, the colour and condition of the rectal mucous membrane should next be noted and a careful search made for pathological lesions, such as carcinoma, ulceration or polypi. Particular attention should be paid to the nature of the rectal contents. The presence of dark blood and mucus in the lumen of the bowel is an ill omen. With all older patients and in cases of doubt, examination by sigmoidoscopy and radiography is indicated.

Internal piles are enlargements of the *columnæ rectales* from dilatation and engorgement of the companion veins of the terminal branches of the superior hæmorrhoidal artery. They are found just above the white line which marks the junction between the skin and mucous membrane of the anal canal. Each pile should be examined in turn.

Ernest Miles, one of the protagonists of rectal surgery, divided piles into three groups (Figure I) and described three primary piles: the left primary pile, the right anterior primary pile and the right posterior primary pile. With these primary piles are associated a number of secondary piles. The groups are as follows:

Group 1.—The right anterior primary internal pile. This pile is always discrete and never has any connexion with neighbouring piles.

Group 2.—The right posterior primary pile with two satellites, the right and the posterior secondary piles.

Group 3.—The left primary pile with two or, rarely, three satellites, namely, the left posterior, the left anterior and the anterior secondary piles.

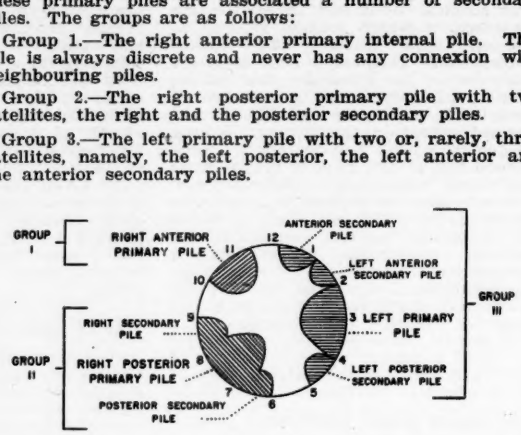

FIGURE I.
Diagrammatic representation of the primary and secondary piles.

Milligan has described three parts to a fully developed pile (Figure II): the pedicle above, covered by pink rectal mucosa; the internal pile itself, covered with reddish strawberry-coloured or plum-coloured mucosa ending abruptly at the white line; and immediately below the white line, the external portion of the pile, covered at first by smooth, shining skin of the anal canal and below by ordinary hairy skin, which may overlie dilated perianal veins and on which skin tags or puckerings may be present. The mucous membrane covering the piles is quite insensitive, in sharp contrast to the skin below the white line.

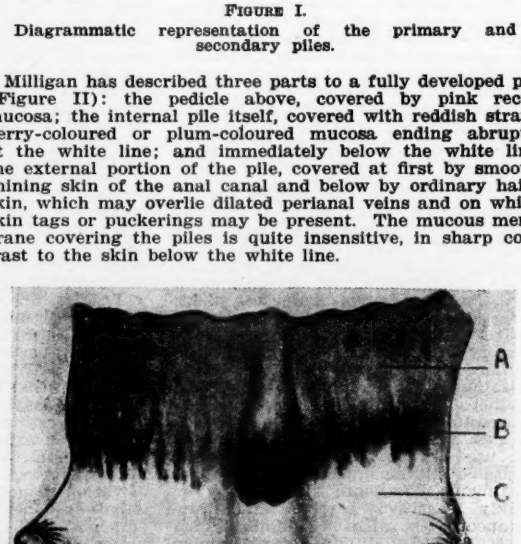

FIGURE II.
The fully developed pile. (From "British Surgical Practice", by E. R. Carling and J. P. Ross (Butterworth).) A, rectal mucosa covering the pedicle of the pile. B, anal mucosa covering the internal pile. C, skin of anal canal. D, skin of anus covering the external hæmorrhoid.

External Piles.

The name "external pile" is sometimes used to describe the external portions of internal piles. The term, however, is a loose one. It is also used to describe other conditions, such as skin tags, the sentinel piles of anal fissure and subcutaneous extravasations of blood (thrombosed external piles)—lesions which have little in common beyond their anatomical situation.

Treatment of Internal Piles.

Indications for Treatment.

Internal piles can be classified into four degrees (see Table I). With piles of the first degree or primary stage, painless hæmorrhage at stool is the only symptom. For

their treatment injection is sufficient. With piles of the second degree or early intermediate stage, hæmorrhage occurs at stool with occasional prolapse. Manual replacement of the piles after stool may at times be necessary. For these, treatment by injection also gives good results. With piles of the third degree or late intermediate stage, hæmorrhage may be slight or absent; prolapse at stool is the main symptom. Prolapse also occurs at other times, on extra exertion or on bending, walking or prolonged standing. For piles of this degree, operation is the treatment of choice, except in the aged or if operation is contraindicated. Some patients with this degree of piles themselves elect injection in preference to operation. In such cases, after temporary improvement, recurrence is usual and reinjection or operation is necessary. Piles of the fourth degree, or final stage, are permanently prolapsed and partly keratinized. They give rise to a bloody discharge, which stains the patient's underclothing and may require the use of a pad. The only treatment of any permanent value is operation.

Piles are often severe during pregnancy, but treatment during this period should ordinarily be deferred until after parturition, when they usually subside and disappear. No operative treatment or injection should at any time be carried out on internal piles which are inflamed or thrombosed.

Treatment by Injection.

The treatment of piles by injection, once a discredited popular method, practised by lay practitioners and itinerant pile doctors, has now established itself as the treatment of choice for about 90% of sufferers. Injection acts by causing thrombosis of the vessels of the pile and fibrosis of the submucous tissue. This leads to contraction and adhesion of the pile to the underlying tissues. Patients suffer little or no discomfort from this treatment and are able to continue their usual life and employment whilst it is being given. The results are uniformly good, and in piles of the first and second degrees they are immediate and permanent. Treatment by injection is contraindicated and harmful for external piles or when the piles are inflamed or thrombosed. Piles complicated by anal fissure, fibrous polypi, pectenosis, fissure or fistula are more suited to the knife than the needle.

The technique of injection has become more or less standardized. It requires a competent knowledge of rectal diseases and rectal anatomy. The treatment should be undertaken only by those who have had proper training and experience.

A 5% solution of carbolic acid in almond oil is recommended for injection. It is non-toxic. It gives excellent results and few complications. It should be used only from ampoules properly prepared. Some prefer a 10% solution. Solutions of carbolic acid in glycerin or water and solutions of quinine, which have been advocated, are inferior to carbolic acid in almond oil, as they are liable after injection to cause sloughing and secondary hæmorrhage.

Proper instruments and a good light are essential. Whitcombe's modification of the Graeme Anderson syringe and special needle, Morley's speculum, two pairs of angled nasal forceps, cotton wool swabs, some spirit, "Dettol" or tincture of "Merthiolate" solution, and a good lubricant are required. Water-soluble lubricants, such as "Lubarol" (Burroughs Wellcome and Company) or "K.Y. Jelly" (Johnson and Johnson) are most satisfactory. Aperients should not be taken by the patient on the night before the treatment, as they fill the bowel with fluid fæcal material and make the examination difficult or impossible.

With the patient in either the knee-elbow or the left lateral position, a well-lubricated speculum is passed and the interior of the rectum and the pile-bearing area are examined. The pile to be injected is selected and the point at which to enter the needle is determined. This point should be touched with a little spirit, "Dettol" or "Merthiolate" solution.

The injection should be given into the upper part of the pile, and the point of the needle should pierce the base of the pedicle of the pile where it is covered by pink mucous membrane. This is about 1·25 to 2·5 centimetres (half to one inch) above the white line. The needle should pass into the subcutaneous space, neither too superficially nor too deeply. Only needles made specially for the purpose, with a proper shoulder near the tip to control the depth of insertion, should be used. When injection is made anteriorly, care must be taken to avoid the prostate and urethra. If the needle is properly inserted, it is possible to lift slightly the mucous membrane. About three millilitres of solution should be injected and the actual amount regulated by watching the swelling of the pile during the injection. In some cases as much as five millilitres or more may be given.

Apart from the discomfort of the speculum, no pain should be felt at any stage of the injection. In fact, the insertion of the needle and the injection should not be perceptible to the patient. If at any stage of the injection the patient complains of pain, the needle should immediately be withdrawn. The cause of pain is inserting the needle and giving the injection into the sensitive skin area below the white line. It can cause great pain and distress to the patient which may continue unabated for several weeks.

Troublesome bleeding can arise from the needle puncture, particularly if the point of the needle enters the pile itself, where it is covered by plum-coloured mucous membrane just above the white line. Injection into the thickened site of a previous injection also is apt to cause free bleeding. If bleeding continues in spite of local pressure through the speculum, it can usually be controlled by packing a gauze swab into the bowel at the site of bleeding, withdrawing the speculum and allowing the gauze to remain for ten to fifteen minutes. The local application or injection of strong solutions of adrenaline at the bleeding point is dangerous and likely to be followed by sloughing and severe secondary hæmorrhage. No patient should be allowed to leave until bleeding is properly controlled. Special care should be taken when an injection is made at the site of a previous injection. Such injections should be carefully watched and immediately discontinued if superficial blanching of the mucous membrane occurs, as in these circumstances sloughing, ulceration and secondary hæmorrhage often result.

TABLE I.

Degrees and Stages of Piles with Indications for Injection and Operation

Degree.	Stage.	Symptoms.		Treatment.	
		Bleeding.	Prolapse.	Injection.	Operation.
1	Primary	+++	−	+	−
2	Early intermediate	++	+	+	−
3	Late intermediate	+	++	−[1]	+
4	Final	−	+++	−	+

[1] "+" in the aged or if operation is refused or contraindicated.

Inject first the largest pile present. As a routine method, one may inject the right anterior pile at the first visit, the left group of piles on the second visit and the right posterior group on the third. Any further injections may then be given at later visits where they are found on examination to be required. Each injection should be charted. From three to five are usually required. They may be given at intervals of from four to seven days. Very little after-treatment, beyond instructions in the care of the bowels, is needed, and the patient can follow his normal life. Complications are rare in the hands of the expert.

Operative Treatment.

The removal of piles or hæmorrhoidectomy is one of the earliest known operations of surgery and was practised by Hippocrates, Galen and Celsus. There are many different methods of performing the operation, all of which call for a practical acquaintance with the anatomy of the ano-rectal region and a sound understanding of the principles of plastic surgery. The best known methods are removal by clamp and cautery, excision, the ligature operation, and excision of the pile-bearing area (Whitehead's operation). Hippocrates used the clamp and cautery and Galen a linen ligature.

The operation here described is a modification of the St. Mark's Hospital ligature method, which itself is based on an operation originally introduced by Salmon in 1833, at the time the hospital was founded.

The simplest pre-operative preparation gives the best results. The patient should be admitted to hospital on the day prior to operation and should have a non-residue diet for at least twenty-four hours. To obtain an empty rectum no aperient should be given within thirty-six hours of the operation nor any enema or washout within twelve hours. The only bowel preparation necessary is a soap and water enema on the evening before operation. The perineum should be shaved; some surgeons shave only the perianal

region, whilst others omit shaving altogether. Sedatives and other premedication are given as ordered.

Some surgeons give a course of antibiotics or sulphonamides by mouth or of antibiotics by injection for several days prior to operation. There seems little indication for this except in special circumstances, such as the presence of fistulæ. At most an injection of the antibiotic immediately before operation and one or two after operation should be sufficient. "Chloromycetin" or terramycin can also with advantage be applied locally to the cut surface, if left open, at the conclusion of the operation.

The anal area and perineum should be swabbed with spirit, tincture of "Dettol" or "Merthiolate" and a careful digital and proctoscopic examination be made. If a sigmoidoscope is to be passed, this should be done at this stage. Any tightness or constriction of the anal orifice should be dealt with by gentle dilatation. Dilatation is carried out routinely by many surgeons, but its extent should not exceed the width of two fingers. Some surgeons evert the piles by packing roll gauze into the bowel through a proctoscope and withdrawing it after removal of the proctoscope.

Each of the primary piles with its accompanying secondary piles should be grasped by pile clamps. Three clamps will be needed, of which two will be placed on the right and one on the left. If the anus is regarded as a clock, with the patient in the lithotomy position, the clamps will be placed at 3 o'clock, 7 o'clock and 11 o'clock (Figure I).

Low spinal anæsthesia with heavy "Percaine" solution is the best form of anæsthesia from the point of view of the surgeon, but patients usually prefer to receive thiopentone. This may be given alone or used for induction, followed by ether, or be combined with a relaxant. There is slightly more bleeding and blood loss with thiopentone than with spinal anæsthesia. Local anæsthesia has disadvantages, whilst the gaseous anæsthetics do not suit this operation.

Practices differ in regard to the position of the patient for operation. The left lateral position has its followers. In the United States, the use of the inverted jack-knife position is almost universal. The British school favours the lithotomy position, often with the addition of the perineal table, at which sits the surgeon with his assistant standing on his left and his theatre sister on his right.

The whole operation should now be planned. Before an attempt is made to remove any of the piles, small scissors cuts should be made above and below each pile to indicate the site at which the intended excision will cross the anal margin and leave sufficient skin and mucous membrane between the excised piles to prevent post-operative stricture or stenosis.

Beginning with the left group (the 3 o'clock clamp), each pile group should be stripped, crushed at its base and tied off and the tie cut long. With the clamp in the left hand, the forefinger inside the rectum beneath the pile, and a pair of strong scissors in the right hand, the surgeon should outline an area of skin which includes the external part of the pile and any skin tags. The skin should then be dissected inwards with the scissors. The cut must be superficial to the circular fibres of the external sphincter, which should be clearly exposed as a broad arc of muscle fibres at the anal margin. The mucous membrane at each side of the pile should be then divided, care again being taken that sufficient will be left. The pile will now be attached only by a pedicle of mucous membrane. This should be crushed by an angioclast with interlocking jaws and the site of the crush transfixed and tightly ligated with strong plaited silk. If the pedicle is thick, it should be divided into two or three parts and each tied separately. The ties must be very tight; a loose tie will make it difficult for the pile to separate later and cause considerable pain or secondary hæmorrhage during convalescence. The bleeding points in the raw area should now be secured and tied with catgut.

The 11 o'clock or right anterior pile is similarly treated and then the 7 o'clock or right posterior group. Any extra piles or projections of mucous membrane are then grasped by forceps, crushed at the base with the angioclast and tied off with heavy silk. Bleeding is again carefully checked. Occasionally, to secure hæmostasis, it may be necessary to suture the stump of a pile to the skin with a mattress suture. The piles are then cut off, care being taken that sufficient is left beyond the ligatures to prevent slipping. "Chloromycetin" or terramycin is then applied to the raw surfaces. This assists in the relief of post-operative swelling and pain. Ointments suitable for application to raw surfaces for superficial anæsthesia, such as "Diothane", may also be used. The wounds should be left open and should at the anal margin present the appearance of a three-leafed clover.

A finger should now be passed into the rectum to make sure that the mucous membrane has not been narrowed by the ties. If so, it should be gently dilated. The cosmetic appearance of the wound is important, and with a pair of curved scissors any skin tags or projections should be trimmed flat. If there is no further bleeding, a piece of gauze should be passed into the anal orifice and a pad and "T" binder applied.

With the ligature operation, it is always advisable to put this small piece of gauze (some favour paraffined gauze) into the anus to control oozing. The older method of inserting a rubber "flatus" tube with paraffined gauze rolled round it is no longer in fashion. By some, a soft Penrose drain is used. Hæmostatic dressings and gauzes offer no advantages and are indicated only if the control of hæmorrhage is difficult.

Post-operative pain can be minimized by proper operative technique and care during the after-treatment. There should be minimal trauma, clean surgical dissection and no undue tying, sewing, or distortion of muscles. Other steps can also be taken. These include the local application of "Chloromycetin" and terramycin or the application of anæsthetic ointments, such as "Diothane", which have already been mentioned. Dilatation of the anal sphincter is also effective; but at most the dilatation should be moderate. Division of the superficial fibres of the external sphincter in the mid-line anteriorly or posteriorly is also of value, particularly if a fissure has been present. There is a slight risk of causing weakness of the sphincter, which is lessened if any dilatation of the sphincter to be performed is carried out before, not after, the muscle is cut.

The injection of anæsthetic solutions in oil at operation has also had some vogue, but has never gained much popularity owing to its obvious risks. At the moment, other solutions for local injection, with long anæsthetic action, are being advocated, but it is yet too early to form any judgement of their value.

Within recent years, closure of the wounds after hæmorrhoidectomy has been advocated. The principles of surgery never change, and the same principles apply here as elsewhere in the body against the closure of soiled or infected wounds and the burying of ligated stumps, which even strenuous use of the sulphonamides and antibiotics cannot obviate. After closure a higher morbidity must be expected. Abscesses, sinuses and fistulæ are the logical outcome in a proportion of cases—complications which do not occur with open methods.

Post-Operative Management.

Morphine should be given post-operatively to relieve pain, and the patient's bladder should be catheterized in six to eight hours if he feels uncomfortable and has not passed urine. He should remain in bed the day of operation and be allowed out of bed on the second day; his stay in hospital should be ten days. This time is necessary to regulate the bowels and covers the period during which there is any risk of hæmorrhage. The gauze placed in the anal orifice at operation should be gently and carefully removed within twenty-four hours. The patient should take baths daily from the third day. Very light dusting of the wounds daily with "Chloromycetin" or terramycin is advised. The patient should be free of pain or discomfort, apart from some pain immediately after the operation, during removal of the gauze and at the first action of the bowels. The bowels should be opened about the third or fourth day, and if pain is to be avoided, care is needed in the choice of aperient. Liquorice powder (*Pulvis Glycyrrhizæ Compositus* B.P.), which consists mainly of senna and sulphur, is advised. It gives a soft easy motion and is the least painful of all the aperients. It is preferred to paraffin, favoured by many, which is inert and acts only by virtue of added phenolphthalein. Two or three teaspoonfuls should be given on the third evening, and if there is no motion next day, four to six ounces of olive oil should be run into the bowel, followed about an hour later by a soap and water enema. A hypodermic injection of morphine should be given at the same time as the olive oil. The bowels should then be kept open every second day by liquorice powder, or an enema if necessary. The use of anæsthetic ointments to relieve the discomfort of the first motion has not proved satisfactory as the patients strain to pass their ligatures, damage the wounds and cause them to bleed.

The post-operative diet is important, and should be of a light non-residue type. Oatmeal and porridge, so often given to these patients, tend to cause fæcal impaction. Pure milk and artificial milk preparations also cause hard fæces and hard feelings,

Retention of urine is a common immediate complication of the operation. The patient should first be allowed to try to pass his urine standing beside the bed. Many surgeons and nurses have an unwarranted fear of post-operative catheterization. It is an atavistic phobia of a past decade, which, whatever foundation it may have had in the past, has little justification in the present. The dangers of over-distension of the bladder today are infinitely greater than the dangers of early catheterization; and as soon after the operation as the patient feels uneasy, his discomfort should immediately be relieved instead of being temporarily lulled by injections of morphine. If the retention persists, an indwelling catheter should be used for some days.

Patients who have had retention of urine and whose bladders have been allowed to become over-distended, particularly if they are old, often lose the power completely or partially to empty their bladders for some time afterwards. These patients should be carefully examined for residual urine, and, if it is present, their bladders should be catheterized several times daily until the bladder musculature regains its tone.

Reactionary hæmorrhage within the first twelve to twenty-four hours is usually derived from small vessels in the external skin wound. The blood is bright and stains the dressings. The bleeding point can usually be seen on careful inspection, secured and tied under local anæsthesia, under-run with a stitch or controlled by the local application of thrombin.

Delayed secondary hæmorrhage is a more serious type of bleeding, which occurs about the ninth or tenth day. The usual cause is tearing of a pedicle which was not tied sufficiently tightly at operation or was too thick or not crushed before it was tied. The bleeding takes place inside the rectum, and the patient passes large motions of dark, semi-clotted blood mixed with fæces. There may be syncope, dizziness and signs of internal hæmorrhage. The occasion is not one for indecision. The patient's blood should be typed for transfusion and he should be taken to the operating theatre for operation without hesitation or delay. Often the actual bleeding point cannot be found, but the hæmorrhage can usually be controlled without difficulty by a series of mattress sutures between the bleeding pedicle and the skin. Packing should be inserted, and the patient should be given antibiotics by mouth and injection to prevent infection.

Of the complications which occur after the patient leaves hospital, fæcal impaction is not uncommon. Improper diet and management in the immediate post-operative phase are predisposing causes. It worries the patient, who makes constant ineffectual attempts to pass the impacted fæces until relieved by enemata.

Patients also complain at times after the operation that they can feel œdematous tags at the anal margin, and special care should be taken at operation to remove all skin irregularities which might form these tags. In most cases they soften and subside within four to six weeks; but if they persist and annoy the patient, they should be removed under local anæsthesia.

Stenosis at the anal margin is due to the removal of too much skin; stricture higher in the bowel is due to the removal of too much mucous membrane. Some surgeons make a practice of passing a finger into the rectum to dilate the anal canal during the early post-operative period. This is a most painful procedure. If the operation has been properly planned and executed, this examination should not be necessary before four to six weeks after the operation. If there is then any narrowing, the examination may be momentarily painful, but in the majority of cases it will cause no discomfort. If any stenosis or stricture is present, several dilatations at intervals of about a month or so are usually all that is necessary.

The operation is almost without mortality and the results are uniformly good. Patients, after operation, should not be allowed to revert to bad pre-operative habits of daily doses of aperients and paraffin. They should be instructed that the taking of aperients is not natural or necessary and that, by a little training and effort, a regular daily action of the bowels can be made a conditioned reflex. It is my practice to give the patients the following instructions.

1. Avoid the regular use of aperients. Do not allow yourself to become addicted to paraffin or pills.

2. The bowel can be trained to act regularly without aperients by observing the following rules: (*a*) Acquire the habit of soliciting an action of the bowels at a regular time each day, whether there be the desire or not. The best time is in the morning in the interval between getting up and dressing. (*b*) Soon after getting out of bed in the morning, drink a tumblerful of water, either hot or cold, and follow this before bathing and dressing by a visit to the toilet. (*c*) If there is no result in a short while, try again immediately after breakfast. (*d*) If no regular daily action of the bowels is obtained at first with this regime, it should be persisted with. An occasional dose of aperient may be required until the habit is established, but daily doses should be discontinued.

3. All calls for the bowels to act during the day must be answered immediately, whatever social inconvenience it may entail, and should on no account be neglected or deferred.

4. A full quantity of fluid, at least two or three pints a day, should be taken.

5. To avoid constipation, meals should be regular. The diet should be well balanced and must be sufficient in amount. It should include clear soups, fish, meat of all kinds, poultry, plenty of bread (white, brown or wholemeal, but not too fresh), toast with plenty of butter, scrambled eggs, potatoes, cabbage, cauliflower, Brussels sprouts, French beans, celery, spinach, sweetcorn, salads with an abundance of oils, onions, apples (fresh, stewed or baked), figs, prunes, dates, pears (fresh or stewed), oranges, grapes, bananas, strawberries, rhubarb, jams, marmalade, preserved fruits and cod-liver oil; tea, coffee, cocoa, beer and other beverages may be taken. The following should be avoided: milk (except in tea or coffee), cheese, sherry, aspirin, new bread, pastry, porridge and oatmeal, peas, new potatoes, rice and tapioca.

6. Regular exercise is important with tepid or cold showers followed by sharp friction with a rough towel. If constipation persists, abdominal massage every morning before rising should be tried.

"Attacks of Piles."

What patients commonly refer to as "attacks of piles" are usually acute painful afflictions in the perianal region, such as fissure, ischio-rectal or submucous abscesses, or even pruritus. Most commonly thrombosed piles are the cause. They are of two types—thrombosed external piles and thrombosed intero-external piles.

Thrombosed external piles are localized extravasations of blood in the perianal region which usually appear suddenly during the passage of a hard constipated stool, but may follow the taking of a strong aperient or diarrhœa. They usually present as tender, painful, firm, bluish swellings close to the anal margin. At first the blood remains fluid and then forms a soft and later a hard clot. There are usually thrombi in the adjacent veins. There may be a single clot, as small as a millet seed or as large as a finger nail, attached to the skin or lying free beneath it. In some cases the swelling is larger and œdematous without the usual blue coloration. In these cases careful palpation may reveal several separate firm clots very much like peas in a pod within the swelling. These may be mistaken for intero-external thrombosed piles.

Thrombosed external piles are the only form of piles common in young people. They are the type which are popularly supposed to follow sitting on cold stones and damp ground. They are in no way related to internal piles, nor do they indicate their presence.

If the patient is seen early, surgical measures should be taken to evacuate the clots. With the patient under local anæsthesia, a radical incision should be made over the swelling, and the clot, which is usually encapsuled, evacuated or removed. If several clots are present in the one swelling, an incision may be made over each clot. All clots including thrombi in the small vessels should be completely excised or turned out. The wound should then be powdered with "Chloromycetin" or terramycin and preferably left open, although at times a tie or several interrupted sutures may be required for hæmostasis. Sometimes the removal of the whole swelling with the overlying skin is necessary. This prevents the later formation of a tag which may worry the patient.

Although the operation is a small one and often described as an "office" procedure, it is best carried out in hospital with proper premedication and with the patient remaining a few hours or overnight. For nervous patients, thiopentone anæsthesia should be used. Some surgeons inject oil-soluble local anæsthetics under the wound, but if all clots have been thoroughly turned out, pain is negligible and prolonged anæsthesia is unnecessary.

If the patient is not treated promptly by operation, there may be severe pain for several days, after which natural cure by spontaneous evacuation of the clot may occur. In most patients the swelling is slowly absorbed, with gradual

diminution of the pain and discomfort, the process taking from four to six weeks. Usually a skin tag remains to mark the site.

If the lesion is not seen until five to seven or more days after its first appearance, the clot is usually adherent. In this case, if the pain is subsiding, *Unguentum Gallæ cum Opio* or ichthyol 10% in glycerin should be applied; but if the swelling is still tender and painful, excision *en bloc*, as previously described, is advisable.

Some patients suffer from recurrent attacks of thrombosed external piles or fissure. They are usually found to be habitual drinkers of large quantities of milk, which causes a hard type of constipation, for which they usually take large daily doses of liquid paraffin. The attacks disappear as soon as the milk-drinking habit is discontinued. It is a clinical entity which almost merits the title of "milk-drinkers' and paraffin-takers' disease".

Thrombosed intero-external piles occur as large protrusions, which involve half or the whole of the circumference of the anus with considerable perianal œdema. The affected part of the anal orifice is usually everted, and on its medial side firm, swollen, inflamed and thrombosed internal piles may be seen.

In these cases the patients should be put to bed with the foot of the bed raised. Ichthyol, 10% in glycerin, *Unguentum Gallæ cum Opio* or "Eusol" packs should be applied locally. Hot foments should be avoided. The antibiotics are of great value in this condition and greatly relieve pain. Penicillin should be given by injection and chloramphenicol or terramycin powder applied locally. Local applications of the sulphonamides should not be used.

Operation is contraindicated. It is a common mistake for the medical attendant to regard the condition as one of prolapsed internal piles and make futile attempts to return them into the anal canal. Anæsthetics are often given for the purpose. Great damage and bruising are often caused, and the swelling invariably returns, often larger than before.

Thrombosed intero-external piles are not necessarily an indication for later hæmorrhoidectomy. The attacks not infrequently result in natural cure.

Acknowledgements.

I am indebted to Mr. Woodward-Smith for the photograph and diagram.

V. M. COPPLESON,
Sydney.

Medical Societies.

THE MEDICAL DEFENCE SOCIETY OF QUEENSLAND.

ANNUAL MEETING.

THE annual meeting of the Medical Defence Society of Queensland was held at British Medical Association House, 225 Wickham Terrace, Brisbane, on Wednesday, March 4, 1953, at 4.30 p.m., the President, Dr. Neville G. Sutton, in the chair.

Annual Report.

The annual report of the Council for the year ended December 31, 1952, was presented and adopted. The report is as follows.

The Council of the Medical Defence Society of Queensland has pleasure in presenting the fifty-first annual report for the year ended December 31, 1952.

Membership.

The Society has now a membership of 584, as against 551 last year. During the year 52 new members were elected and one was reinstated. Our losses were: deceased 5, resigned 6, left the State 9.

Obituary.

It is with much regret that we record the deaths of the following members: Dr. D. A. Carter, Dr. H. V. Foxton, Dr. H. B. Skinner, Dr. Joyce S. Stobo, Dr. H. A. Sundstrup.

Office Bearers and Council, 1952.

The following office bearers were unanimously reelected by the Council: *President*, Dr. Neville G. Sutton; *Vice-President*, Dr. G. W. Macartney; *Honorary Treasurer*, Dr. T. V. Stubbs Brown; *Honorary Secretary*, Dr. R. G. Quinn; *Councillors*, Dr. T. R. Biggs, Dr. H. W. Horn, Dr. F. W. R. Lukin, Dr. H. Masel, Dr. Athol Quayle, Dr. F. Garrett Scoles, Dr. J. G. Wagner.

Dr. G. W. Macartney, Dr. R. G. Quinn and Dr. F. Garrett Scoles, who retired in conformity with the by-laws, were reelected to the Council. Dr. T. R. Biggs was elected to fill a vacancy on the Council.

Medico-Legal.

A further two cases were submitted to the Society during the year. One case involves two medical practitioners, one of whom was not covered by indemnity insurance at the time the cause of action is alleged to have occurred. Both cases are still pending.

No further action has been taken in one of the cases which was referred to in the last annual report.

Indemnity Insurance: Medical Protection Society, Limited.

Of the 584 members, 13 have indemnity insurance cover with other approved corporations, in accordance with the articles of association of the Queensland Society. The arrangement which exists with the Medical Protection Society, Limited, has continued to work very satisfactorily, and in view of the prevailing high damages given by juries, many members have increased their cover to ensure adequate protection.

Finance.

It will be shown from the balance sheet that the net surplus for the year ended December 31, 1952, amounted to £315 7s. 4d.

Some items of income and expenditure are as follows:

Receipts—	£	s.	d.
Annual subscriptions to the Medical Defence Society of Queensland	296	5	9
Entrance fees	52	10	0
Subscriptions, indemnity insurance	2,790	0	6
Interest:			
Commonwealth Government Treasury Bonds and Inscribed Stock	284	17	4
Commonwealth Savings Bank	10	18	9

Expenditure—	£	s.	d.
Amount remitted to Medical Protection Society	2,777	0	5
Secretarial and clerical assistance	204	0	0
Printing and stationery	49	14	6
Rent, postage, duty stamps, bank changes and sundries	32	6	0
Accountancy and audit	13	13	0
Federal income tax	48	6	0

The total assets of the Society amount to £8623 7s. 11d.

An amount of £7663 18s. is invested in Commonwealth Government Inscribed Stock.

Current assets include bank balances amounting to £950 6s. 6d.

NEVILLE G. SUTTON,
President.

Balance Sheet and Financial Statement.

The balance sheet and financial statement for the year ended December 31, 1952, was adopted.

Election of Councillors for 1952.

The following councillors, who had retired in rotation in accordance with the by-laws, were reelected: Dr. Neville G. Sutton, Dr. Athol Quayle, Dr. H. Masel.

Election of Auditors.

Messrs. R. G. Groom and Company, Chartered Accountants (Australia), were reelected auditors for the ensuing year.

Membership.

It was resolved that it be a recommendation to the Council that a canvass should be made to increase the membership of the Society.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

UNIVERSITY INTELLIGENCE.[1]

[*Australian Medical Gazette*, May, 1870.]

THE Professorial Board of the University has recently, we understand, agreed to a resolution nominally for the purpose of shutting out colonial and foreign graduates from the right of admission to *ad eundem* degrees in the University of Melbourne, but in reality to exclude from our local *alma mater* the graduates of the University of Sydney. The real objects of the gentlemen composing the Professorial Board, although too shabby and contemptible to be avowed, are patent enough. It is almost incredible that fine gentlemen—even assuming them to be the quintessence of learning—should be found not only too willing to sacrifice the best interests of the university to gratify the petty spite of some of their number, but hoping to induce others to acquiesce in so suicidal and selfish a policy. The gentlemen who honour the colony by receiving an annual stipend surpassing their most sanguine expectations, until a lucky accident wafted them into the Southern Hemisphere, apparently require to be reminded that the University is founded in the interests of the community at large—is not their private property. It is fortunate that these gentlemen have so easily shown themselves in their true colours. The Professorial Board is evidently frightened out of its propriety at the bare prospect of a few graduates of the University of Sydney being admitted within the sacred precincts where the alumni of St. Andrews, Giessen et cetera *hoc genus omne* have been welcomed with open arms, but from which it is now attempted, by a side wind, to drive away the graduates of a neighbouring university. There is, however, little reason to believe that either the Council or the Senate will permit the University to be made the means of gratifying the vindictive instincts of the members of the Professorial Board. We may remind these gentlemen that the Parliament of Victoria which has just appointed a committee of its members to consider the best means of bringing the Australian colonies into close union, also votes their salaries.

[1] From the original in the Mitchell Library, Sydney.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Week-End Course at Tamworth.

THE Post-Graduate Committee in Medicine, in conjunction with the Northern District Medical Asssociation, will hold a week-end course at Tamworth on Saturday and Sunday, June 27 and 28, 1953. The programme is as follows:

Saturday, June 27, at the Tamworth Base Hospital: 2 p.m., registration; 2.30 p.m., panel discussion on "Thyroid Disease", Dr. K. B. Noad, Dr. J. Chesterman, Dr. F. F. Rundle; 4.15 p.m., "Endometriosis. Practical Aspects of the Rh Factor", Dr. J. Chesterman.

Sunday, June 28, at the Tamworth Base Hospital: 9.30 a.m., "Useful Drugs in the Treatment of Disease of Nervous System", Dr. K. B. Noad; 10.15 a.m., "Œsophageal Obstruction: Investigation, Diagnosis and Management", Dr. F. F. Rundle; 11.30 a.m., "Latest Views on Toxæmia of Pregnancy", Dr. J. Chesterman; 12.15 p.m., local lecturers; 2 p.m., "Some Clinical Observations on Gastric and Biliary Surgery", Dr. F. F. Rundle; 2.45 p.m., "Meningitis, Recognition and Treatment", Dr. K. B. Noad; 3.30 p.m., local lecturers.

The fee for attendance at the course will be £3 3s. Those wishing to attend are requested to notify Dr. G. Archbold, "Baranbali", Bridge and Denne Streets, West Tamworth, 4N, as soon as possible. Telephone: Tamworth B 351.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED APRIL 4, 1953.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	..	5(1)	..	..	..	..	..	..	5
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	..	..	..	..	3	..	3
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	1(1)	..	..	..	..	..	..	..	1
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	1(1)	1(1)	15(9)	..	..	..	1	..	18
Diphtheria	19(11)	4(1)	4(2)	..	1(1)	..	..	..	28
Dysentery (Bacillary)	..	5(5)	..	3(2)	..	..	..	..	8
Encephalitis	..	1(1)	..	..	..	..	..	..	1
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	..	4(1)	..	..	4(2)	..	1	..	9
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	1	..	..	..	..	..	1
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	..	..	..	..	1	..	..	..	1
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	10(7)	8	9(2)	13(5)	1(1)	1(1)	..	..	42
Puerperal Fever	..	..	..	..	1	..	..	..	1
Rubella	..	9(3)	1	..	4	..	..	..	14
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	8(4)	66(35)	1(1)	2(1)	2(2)	..	..	2	81
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	2(2)	..	..	..	..	..	2
Trachoma	..	..	..	..	..	..	..	..	..
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	29(23)	38(23)	5(2)	7(6)	6(2)	1(1)	1	..	87
Typhoid Fever	..	..	1(1)	..	1	..	..	..	2
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

Annual Subscription Course.

The Post-Graduate Committee in Medicine in the University of Sydney announces that Dr. Gladys Dodds, M.D., D.P.H., F.R.C.S., F.R.C.O.G., will be visiting Sydney in May when she will give a lecture on "Hypertension in Pregnancy" on Thursday, May 14, 1953, at 8.15 p.m. in the Stawell Hall, 145 Macquarie Street, Sydney. Dr. Gladys Dodds is Honorary Obstetrician and Gynæcologist, Hackney and Mile End Hospitals, and Honorary Obstetrician, Mothers' Hospital, Clapton, London, and she is well known for her work on hypertension in pregnancy.

This lecture forms part of the annual subscription course conducted by the Post-Graduate Committee in Medicine, 131 Macquarie Street, Sydney, from whom further details may be obtained. Telephones: BU 5238, BW 7483.

University Intelligence.

UNIVERSITY OF MELBOURNE.

THE nineteenth Beattie-Smith Memorial Lectures on Insanity will be given by R. Stewart Kennedy, M.B., Ch.B. (Glas.), D.P.M. (Lond.), Specialist (Psychiatry), Repatriation Department (Victorian Branch), Melbourne, on May 11 and 18, 1953, in the Anatomy Theatre, University of Melbourne, at 8.15 p.m. The subject will be "Psychiatry in Relation to the Family".

Corrigendum.

IN Dr. W. J. McCristal's letter on heparin therapy in severe coronary atherosclerosis and *angina pectoris* published in the issue of April 25, 1953, an error was made in the seventh line. The words a sthenic were printed as asthenic. We apologize to Dr. McCristal for this error.

Deaths.

THE following deaths have been announced:

ADAMS.—David Joseph Monk Adams, on April 25, 1953, at Sydney.

BRADLEY.—Clement Henry Burton Bradley, on April 22, 1953, at Sydney.

Royal Australasian College of Surgeons.

OPEN MEETING.

A MEETING of the Royal Australasian College of Surgeons will be held in the Stawell Hall, Royal Australasian College of Physicians, 145 Macquarie Street, Sydney, on Wednesday, May 27, 1953, at 8.15 p.m. Mr. E. H. Goulston and Mr. J. Steigrad will speak on "Congenital Atresias and Achalasias". This meeting is open to all members of the medical profession.

Medical Appointments.

Dr. H. R. Bailey has been appointed to the Division of Mental Hygiene in the Department of Public Health, New South Wales.

Dr. A. A. Crooks has been appointed public vaccinator to Manangatang and district, Victoria.

Dr. C. Craig has been appointed a member of the Nurses' Registration Board of Tasmania.

Dr. E. D. G. Kirkwood has been appointed public vaccinator to the Shire of Doncaster and Templestowe, Victoria.

The following have been appointed psychiatrist superintendents in the Mental Hygiene Branch, Department of Health, Victoria: Dr. J. V. Ashburner, Dr. J. F. J. Cade, Dr. H. J. C. Edmonds, Dr. G. A. Goding, Dr. V. P. Johnson, Dr. R. E. G. Maclean, Dr. A. R. Phillips, Dr. T. G. C. Retallick, Dr. E. L. Roberts, Dr. H. C. Stone, Dr. G. A. Wright.

Dr. D. M. Anderson has been appointed a medical examiner of the State Psychological Clinic of Tasmania.

Dr. D. L. Walker has been appointed public vaccinator to the Shire of Colac, Victoria.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

McLaughlin, John Mannix, M.B., B.S., 1952 (Univ. Sydney), 729 Old South Head Road, Vaucluse, New South Wales.

Diary for the Month.

MAY 12.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
MAY 15.—Queensland Branch, B.M.A.: Council Meeting.
MAY 18.—Victorian Branch, B.M.A.: Finance Sub-Committee.
MAY 19.—New South Wales Branch, B.M.A.: Medical Politics Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in the Commonwealth can become subscribers to the journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £5 *per annum* within Australia and the British Commonwealth of Nations, and £6 10s. *per annum* within America and foreign countries, payable in advance.